American Journal of Obstetrics and Gynecology

VOL. 34 DECEMBER, 1937 NO. 6

Original Communications

THE PREVENTION OF ECLAMPSIA*

PROF. K. DE SNOO, UTRECHT, HOLLAND

BEFORE beginning my lecture, I wish to express my deep sense of indebtedness to your President for his invitation to speak here in your midst, and for the honor he has conferred, through me, upon our Dutch Gynaecological Association.

I assure you that we greatly appreciate the friendly feelings which you have thus shown to our country.

When your President asked me to submit 2 or 3 subjects, I did not hesitate to include among them the prevention of eclampsia, because it is my firm conviction that eclampsia can almost certainly be prevented. For, as I hope to be able to demonstrate, we are not merely in a position to recognize the danger of eclampsia in time by a regular examination of the gravidas, but by means of a diet minus salt, in conjunction, if need be, with narcotics and venesection, we have the almost infallible means of preventing the occurrence of convulsions. And in saying this, I speak from an experience of twenty-five years.

In speaking about eclampsia it is essential to know exactly what we understand by this term.

As the word expresses, this was originally understood to mean a pathologic condition in a pregnant or postpartum woman, characterized by convulsions. Later on, however, the opinion that the convulsions were caused by kidney troubles (nephritis) led to the idea of embracing severe albuminuria, accompanied by uremic symptoms, such as head-

*Read, by invitation, at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

aches, vomiting, and impaired eye sight, and in the international list of "causes of death," eclampsia and albuminuria are even still classed together.

In my opinion this is a mistake; cause and result have here been confused, which is one of the chief reasons why eclampsia is still the illness of theories. In other words, a problem yet unsolved—so far as we can ever speak of a solution to a biologic problem.

We may safely assume at the present time that during pregnancy a number of changes take place in the body under the influence of the metabolic products of the ovum and of the placenta in particular. Further, that these changes, which have come about by selection in the course of millions of years, enable the organism to fulfill its function of propagation, in the widest sense, quite well without harm to the organism itself.

Whenever this is the case, i.e. whenever under the influence of the products of gestation, abnormal reactions occur, we have to do with a morbid condition to which for more than forty years we have applied the term toxemia of pregnancy.

The origin of this term lies in the idea that the kidneys are not able to pass the metabolic products of the child together with those of the mother, whereby first of all the function of the kidneys is impaired, with as consequence the symptoms of uremia, such as headaches, vomiting, etc., and also convulsions.

This idea still holds at the present day, albeit with this difference that it is not the metabolic products of the child, but of the placenta, which are thought to affect the kidneys, and then not even the normal metabolic products of the placenta but special, noxious substances which form under certain circumstances.

This particular toxin, however, has never yet been demonstrated, and in my opinion it is highly improbable that there is any such toxin, if for no other reason than that nearly all gravidas exhibit slight anomalies more or less. This points to there being one general cause of these anomalies, and when we consider that gestation disturbances but very rarely occur in animals, it is obvious that we must look for this cause in the fact that the human being has deviated from nature, i.e. in civilization.

I trust that in the course of this paper I shall be able to convince you that this is indeed the case, and more particularly that it is our custom of salting our food which is on a high degree responsible for these disturbances, especially edema and convulsions.

In how far the hypertension as a rule is partly or wholly a consequence of the consumption of common salt, is not yet certain, for the vascular system is influenced to a high degree by psychic factors, and it is very probable that this accounts in part for the frequent occurrence of hypertension.

At all events the vascular system plays a large part in the pathogenesis of the anomalies of pregnancy, and it is probable that the last cause of the defective functioning of kidneys and liver, and also of the eclamptic attack, is due to vasomotor cramp and the resulting defective circulation.

It is not the object of this paper, however, to inquire thoroughly into the pathogenesis, since it is the prophylaxis which claims our attention today. I will confine myself to the remark that various observations, for instance, the premature separation of the placenta whereby, just as in eclampsia, some times anuria and even necrosis of the renal cortex may be observed, point to the convulsions as causing reflex vascular constriction. This is the reason for the severe albuminuria in women with eclampsia when the spasms last too long and the tissues are particularly sensitive, as also of the bleeding and the necrosis in the liver.

But this same vascular cramp may also arise gradually, without convulsions, as a direct reaction to the pregnancy. And when this vascular cramp lasts long and is severe, and the tissues are sensitive, the same symptoms may appear as in eclampsia, i.e. eclampsism. And now we understand why we have so long thought that eclampsia was the consequence of the diseased kidneys or liver, whereas it is, on the contrary, just the liver and kidneys which become impaired by convulsions. Fig. 1 gives a survey of this theory.

There are several facts which tend to show this.

1. There is no parallelism between the severity of the toxemia and the danger of eclampsia.

In the majority of cases eclampsia occurs even in women who to all appearances had been healthy, and reversely, the number of women with serious toxemia who get eclampsia, irrespective of the therapy, is small.

2. Is the urea percentage in the blood at the moment of the outbreak of eclampsia generally normal, but rises not infrequently some time after the attacks have ceased, while the prognosis of the gestatory albuminuria is independent of whether convulsions have occurred or not?

3. As regards the liver function, we often find that the bilirubin percentage of the blood does not rise until after the attacks.

But this is not all.

After I had studied successively the relation between edema and eclampsia, between albuminuria (and the kidney function) and eclampsia, and between hypertension and eclampsia, I studied the attacks themselves, in a long series of cases (136) (viz. the number, the length of the intervals, the influence of the parturition, of the loss of blood, of narcotics, etc.) particularly in connection with the blood pressure which, for this purpose, was measured every five minutes.

The results were as follows:

1. All attacks are practically similar and purely epileptiform.

2. They occur at fairly regular intervals.

3. They show a tendency to cease spontaneously without any therapy.

4. They are directly dependent upon the blood pressure, in the sense that we are able, by artificially lowering the blood pressure, to lengthen the intervals between the attacks, or to avoid the attacks entirely.

5. The duration of the eclampsia, the number of the attacks and their severity are not dependent upon whether we have to do with eclampsia antepartum, durantepartum, or postpartum; further, the birth of the child has a favorable effect only if a severe afterbleeding follows with an appreciable lowering of the blood pressure.

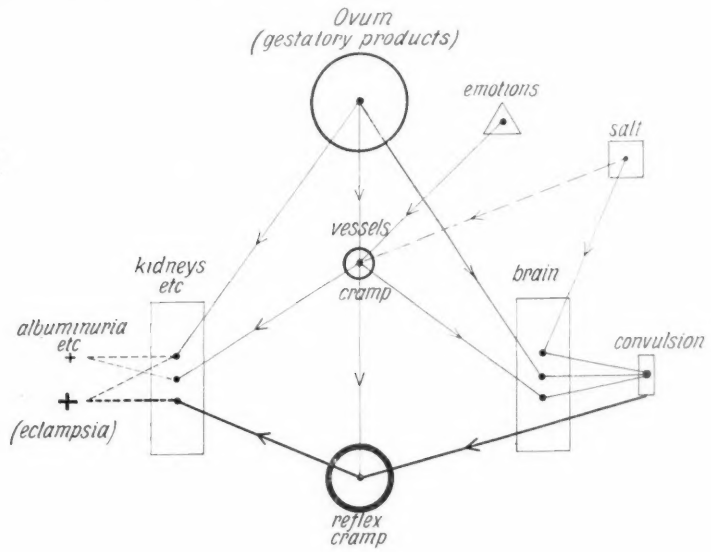

Fig. 1.

6. The course is similar in multiparas and primiparas, in women with normal kidneys and with chronic nephritis.

7. The blood pressure invariably rises immediately after an attack.

We could not, therefore, do other than draw the conclusion that if eclampsia has once made its appearance the attacks are governed by a certain mechanism, which runs, as it were, like clockwork until, after a certain time, on an average twelve hours, it comes to a standstill. And this assumption finds confirmation in a few observations made during the early years when, more than once, a second series of attacks occurred three or four days later, even occasionally followed by a third series. (This was at the time when we were still giving a milk diet. After a saltless diet had been substituted a recurrence never took place, not even in women with intercurrent eclampsia.)

But, if we have to assume a certain mechanism in the occurrence of the attacks, this implies that this mechanism is regulated, and that there must be some center from which such a regulation takes place. And then it is not difficult to see that eclampsia cannot merely be the consequence of irritation of the cortex cerebrum, but of irritation of that center, whereby outbursts result, i.e. the convulsions. And in how far it may come to outbursts in a particular case thus depends on the one hand upon the excitability of this center, and on the other hand upon the presence of special irritants to which the hypothetical center is susceptible (Fig. 1).

In thus presenting the character of the convulsions, it will be clear how incorrect it is to speak of eclampsia and toxemia in one breath, and that we must regard the eclamptic attack as a separate entity of pregnancy, the consequences of which, owing to reflex vascular cramp, are qualitatively the same as toxemia proper, though generally *quantitatively much more severe*, and this is not affected one jot by the fact that in general already prior to the fits there were more or less clear symptoms of toxemia. So it becomes comprehensible why in many cases eclampsia occurs in women who to all appearances are healthy, while, on the other hand, it does not appear by any means in all women who suffer from severe toxemia.

As you will see presently, of about 2,400 women who in the course of time were admitted in the clinic suffering from toxemia, only 54 had eclampsia. And although the measures we took undoubtedly prevented many an attack of eclampsia, yet we may safely assume that of that large number, the greater majority would never have had eclampsia, even without any treatment.

On the other hand, among the women admitted with eclampsia were many who but shortly before had neither albuminuria, nor headache, nor any other pronounced symptoms, and even two normal patients admitted for delivery had eclampsia who not only had no albuminuria or hypertension but no edema either.

Regarded in the light of the theory of a "cramp-center" all this will be clear.

There is thus every reason to keep toxemia and eclampsia distinct, and to understand by the prophylaxis for eclampsia only the prophylaxis for convulsions, that is, of the explosions of the crampcenter.

It has appeared that women who have a normal blood pressure practically never get eclampsia, neither do women who have lived for two or three days on water, or on a diet minus salt. This is of the greatest importance in the practice of the prophylaxis, because in measuring the blood pressure we possess the means of early diagnosing the danger of eclampsia, and on the other hand, as I will show you, by means of water and a salt-free diet, respectively, of averting that danger with almost absolute certainty. I will show you this on this table, which gives a survey of my experience during 30 years (Table I).

TABLE I

	CASES OF TOXEMIA	ECLAMPSIA BREAKS OUT AFTER ADMISSION										
		HOURS			DAYS				WEEKS			
		0-6	6-12	12-24	1-2	2-3	3-4	4-7	1-2	2-3	3-4	
Milk diet (Rotterdam)												
1907	61	1		1	1			2				
1908	59	1	1		1		1	1				
1909	70	1										
1910	65			1								
1911	94	1						1				
5 years	349	4	1	2	2		1	4				14
Salt-free diet (Rotterdam)												
1912	62	2										
1913	69	1		1								
1914	65											
1915	58		1									
1916	82		2	1								
1917	130					1						
1918	70	1									1	
1919	59	1			2							
1920	101	1										
1921	62	3										
1922	77		1		2							
1923	91											
1924	113		1	1								
1925	125				1							
½ y. 1926	56							1				
15 years	1220	9	5	3	5	1		1			1	25
Salt-free diet (Utrecht)												
1927	62					1					1	
1928	75							1				
1929	70		1			1						
1930	73					1						
1931	80											
1932	62	1										
1933	56	2										
1934	76	1										
1935	120	2	2									
1936	142				1							
10 years	816	6	3		1	3		1			1	15

In the first period, 1907 to 1911, I began with a milk diet and gradually changed the milk for salt-free food. In the second and third periods the patient was given exclusively a salt-free diet, with 1 or 2 liters of water extra. Most patients were admitted with the diagnosis of impending eclampsia or with hypertension and albuminuria. However, not more than 54 had eclampsia, and as you see almost the same frequency on milk as on a salt-free diet which, in my opinion, goes to prove that in a great number there was no danger of eclampsia at all. Still, in others this would have been the case, but now you see that of 348 women on a milk-diet, 5 after three days developed eclampsia as against only 4 of 2,000 women who had been given a salt-free diet, and in each of these 4 cases it can be demonstrated that mistakes had been made with the diet.

Moreover, these women had but 1 or 2 attacks, so that the treatment had not been quite unavailing.

This, in my opinion, establishes the important significance of the salt-free diet.

But to obtain good results, the diet must be carefully prescribed, and strictly adhered to and controlled. This frequently involves some difficulty, either because the physician or the nurse is not wholly convinced of its infallibility, or because the patients, consciously or unconsciously, make mistakes. In this respect it may be worth mentioning that when I took over the management of the Clinic at Utrecht with the old nursing staff, it took three years of hard work before I had banished eclampsia.

This use of this word is justified by the fact that in the last seven years not a single case of eclampsia has occurred in my Clinic later than two days after the patient had been admitted.

The easiest method of determining the NaCl in the urine is with the chlorometer of Strauss, with a graduated test tube.*

As a rule the edema disappears or diminishes with a salt-free diet, though by no means invariably; very occasionally it even grows worse, as the scales quickly show.

After two days however, and that is the important thing, there is no need to fear attacks of convulsions, not even when the symptoms of toxemia increase and the women become seriously ill.

In such cases I do not perform a cesarean section, as has been the practice of recent years, but I induce labor by means of a condom

*The apparatus is filled up to stripe A with the solution of Martius Lüttke, which contains a certain quantity of nitrate of silver and sulphate of iron. (*a.* 17 gr. nitras argenti are to be dissolved in 300 or 400 c.c. aqua destillata and 500 gr. acidum nitricum added. *b.* 40 gr. sulfas ferricus are to be boiled in 100 c.c. water, until it is completely dissolved; then cooled and filtered. *a.* and *b.* are to be joined and supplied with aqua dest. up to 1 liter.) Then it is filled up to stripe U with the urine to be examined and shaken.

The AgCl will then be precipitated and there will remain a surplus of nitrate of silver, which is titrated back again with a solution of sulphocyanate ammonium. (3.9 gr. sulfocyanetum ammonicum on 1 L. aqua dest.)

As soon as the $AgNo_3$ is fixed by the sulphocyanate ammonium, it colors red, the ferrous sulphate acting as indicator.

The quantity of NaCl per liter in the urine is indicated by the number at the stripe to which the fluid reaches.

catheter. The child is then usually born within twenty-four hours, and since the therapy of a saltless diet plus water has been employed, eclampsia has not once occurred in a series of more than 100 patients who had labor induced and who had been so treated for not less than two days previously.

This is the second proof of the importance of the salt-free diet. A third proof is the fact that in women with intercurrent eclampsia, i.e. in women whose attacks had ceased before labor began, a second or even a third series of attacks never occurred, as used to happen repeatedly in the first periods, with a milk diet.

A diet minus salt is therefore much to be preferred to a milk diet (although by this I do not mean to say that a milk diet may not be useful). Milk, however, contains 1.7 gr. of NaCl per liter, so that in the consumption of 4 liters per day about 7 gr. of salt are consumed, against only 1 or 2 gr. with a salt-free diet. Apparently this quantity is still too high in some cases.

In food salted in the usual way we consume 15 or 20 gr. of NaCl per day. And herein lies the last cause of eclampsia. We salt our food to make it palatable. And it is this salt that we must up to a point regard as the eclampsia toxin; not what is formed in the body, but what enters from without. If, therefore, all gravidas were to be put on a salt-free diet, there would be practically an end of eclampsia.

This, however, is not necessary, for, as I mentioned above, retention of salt is not the sole condition for the attacks of eclampsia, An increased blood pressure is also an essential, and experience has taught that this can generally be detected betimes, even in out-patients, as I shall presently show you.

But first, a few words respecting the edema and the influence of abstinence from salt upon the composition of the blood. No fewer than 70 per cent of gravidas suffer from edema, and of the others 30 per cent have a preliminary edema, as is evinced by their losing weight, postpartum. If, however, the gravidas are fed upon a salt-free diet there is no edema, nor do they lose weight after the confinement, so that the cause of the edema must be looked for in our custom of salting our food to make it palatable. Meat, butter, cheese, and potatoes are prepared with salt, and the baker uses large quantities of salt in the baking of bread, biscuits, and all kinds of cake. In this way we consume on an average of about 15 gr. of salt extra, and can assimilate this without discomfort.

During gestation, however, the tolerance of NaCl diminishes as pregnancy proceeds, and the tissues retain the salt, which causes water retention, with ensuing edema. But the salt percentage in the blood remains practically unchanged. By abstaining from salt, the tissues set the surplus-salt free, so that the kidneys are able to pass it, and simultaneously the edema decreases or disappears.

Thus, by means of a salt-free diet we were able in many cases to cure the edema completely before parturition, as is best seen by the fact, that the patient does not loose weight postpartum anymore.

In other cases we did not attain a complete cure, and even occasionally the edema increased, notwithstanding the diet, but even in these cases there is after two days no danger of eclampsia.

CASE 1.—Para i, twenty-five years of age, is admitted with strong albuminuria (10 per cent) and considerable edema. Notwithstanding salt-free diet the weight increased, but no eclampsia occurred. Three weeks anteterminum a living child was born spontaneously, after which immediately a large diuresis began and the edema disappeared. As Fig. 2 shows, the weight increased in childbed with 13 Kg.; after taking salted food again, the weight increased with 2 Kg. One sees in the figure, how the NaCl excretion after parturition was much larger than before parturition.

After parturition, the tissues set the salt free, and it is passed with the urine. This is the reason for the increased diuresis generally immediately postpartum, and for the large quantities of salt then passed. You will permit me to illustrate this with an example from my early practice, which made a great impression on me and influenced the direction which my eclampsia researches have taken (Table II).

TABLE II

DATE	QUANTITY	SPEC. GRAV.	ALB. 0/00	ALB. IN 24 HR.	NaCl PER L.	NaCl IN 24 HR.	REMARKS	FOOD
1907 Nov.								
19	670	1023	12.0	8.4				3 liter milk
20	1040	1010	3.5	3.64	7.1	7.38		3 liter milk
21	1240	1014	6.0	7.44	5.0	6.2		4 liter milk
22	550	1037	12.0	6.6	2.0	1.1	Eclampsia	3 liter milk
23	890	1017	5.0	4.45	2.3	3.05		4 liter milk
24	2760	1008	2.0	5.52	2.4	6.62		5 liter milk
25	1300	1010	2.0	2.6	2.5	3.25		4 liter milk
26	1050	1011	4.0	4.2	4.9	5.14	Abortus provocatus	1½ liter milk
27	4870	1010	0.3	1.46	7.0	34.09		3½ liter milk
28	4610	1007	0.5	2.3	8.2	37.8		5 liter milk
29	3460	1011	1.0	3.46	5.6	19.37		4 liter milk
30	2700	1008	1.0	2.7	5.0	13.5		5 liter milk
Dec.								
1	2600	1010	0.5	1.3	8.2	21.35		4 liter milk
2	2450	1010	0.5	1.22	6.0	14.7		4 liter milk
3	2860	1009	0.75	2.14	6.8	18.04		5 liter milk
4	2500	1010	0.3	0.75	9.5	23.7		4 liter milk
5	2280	1011	0.3	0.68	7.4	16.87		3 liter milk
6	2780	1011	0.25	0.69	8.3	23.07		5 liter milk
7	2430	1010	0.2	0.48	8.2	19.92		5 liter milk
8	2920	1009	0.2	0.58	8.8	25.69		5 liter milk
9	2940	1010	Trace		11.8	34.69		5 liter milk
10	2660	1009	Trace		7.3	19.42		5 liter milk
11	3190	1007	Trace		4.6	14.67		5 liter milk
12	2760	1009	Trace		5.2	14.04		5 liter milk
13	3010	1010	Trace		3.8	11.43		5 liter milk
14	1740	1011	None		2.9	5.04		5 liter milk
15	2080	1013	None		2.7	5.61		5 liter milk

This was the case, thirty years ago, of a sixteen-year-old girl who was admitted with severe edema and albuminuria. On a milk diet the edema grew worse; the diuresis was moderate, and the urine contained fairly little salt. After four days she developed an eclamptic attack which did not cause much change in the functioning of the kidneys. Four days later labor was induced and a mole was expelled. Immediately the diuresis increased, already the first day almost 5 liters, and the NaCl percentage also rose so much that in the first week nearly ½ Kilo of salt was passed (Fig. 2).

The increase in the diuresis was so rapid (and this can be repeatedly observed) that the kidneys could not possibly have recovered in so short a time, and thus the edema cannot have been the consequence of the impaired kidney function but must be ascribed to the greater *affinity* for salt of the tissues by reason of the circulating gestatory products.

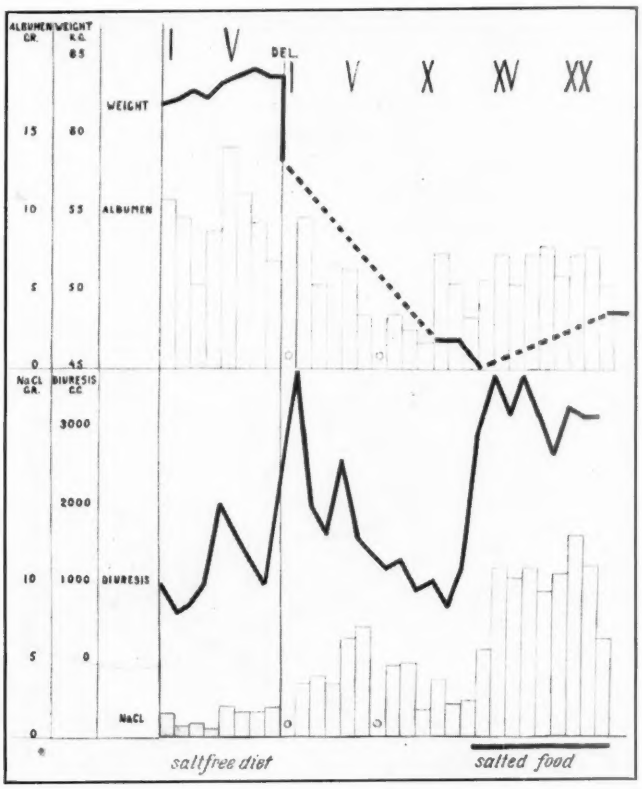

Fig. 2.

That this is actually the case has been proved by examining the influence of a salt-free diet upon the composition of the blood.

For many years, we have examined the Na, K and Ca content of the blood of all our patients with toxemia and eclampsia, in many cases at different times, on admittance and before and after parturition. We have studied the influence of a water and a salt-free diet, respectively, and compared normal nonpregnant women, with normal gravidas, gravidas with toxemia, nephritis and eclampsia.

As a matter of fact the number of investigations amount to about 1,000, all carried out in the same way and by the same person.

These researches have shown:

1. That there is practically no difference between the Na content of the blood, in gravidas and nongravidas and in normal and toxemic women with normally salted food.

2. That on a salt-free diet invariably the Na content diminishes, as well in normal gravidas as in toxemic ones, on an average of 5 per cent (from 333 mg. to 317 mg.) as is seen in Fig. 3, regarding 100 cases of toxemia, where there is a considerable divergency in the figures of the sodium content of the blood in salted and salt-free food.

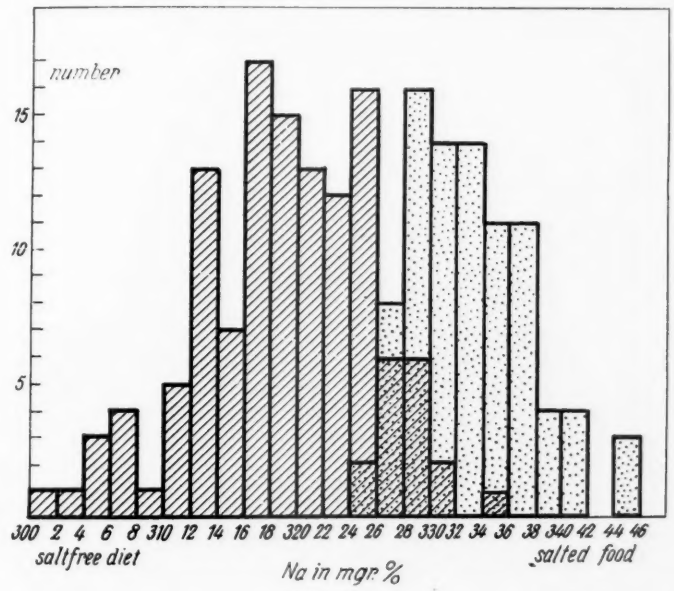

Fig. 3.

3. That in eclampsia the Na content in most cases is approximately normal, but in other cases abnormally high, until 370 mg. and more.

4. That the influence of the salt-free diet on the chlorine content is about the same, as on the Na content.

The calcium and potassium content on the contrary do not change.

The fall of the NaCl percentage is about the same in normal and in toxemic gravidas, in gravidas with and without edema, and is even independent of the fact, whether the edema disappears after water or salt-free diet or not, of whether eclampsia has preceded or not.

It is of great importance, that after parturition in all women the NaCl content of the blood serum temporarily increases, notwithstanding the continuation of the salt-free diet; on an average by 5 mg.

Apparently the tissues retain the salt under influence of the gestatory products; in pregnancy they get a heightened affinity for salt, through

which an accumulation of salt arises, which is the more considerable as the affinity is more intense or the quantity of salt in the blood higher.

It may be that especially the Na combines with the water thereby causing edema, and according to Zangemeister and numerous other authorities, this edema increases the brain pressure and thereby causes convulsions. These researchers even hold edema to be primary and salt retention to be secondary, and therefore lay the chief stress upon the abstinence from liquid. Yet Zangemeister also gave his patients a salt-

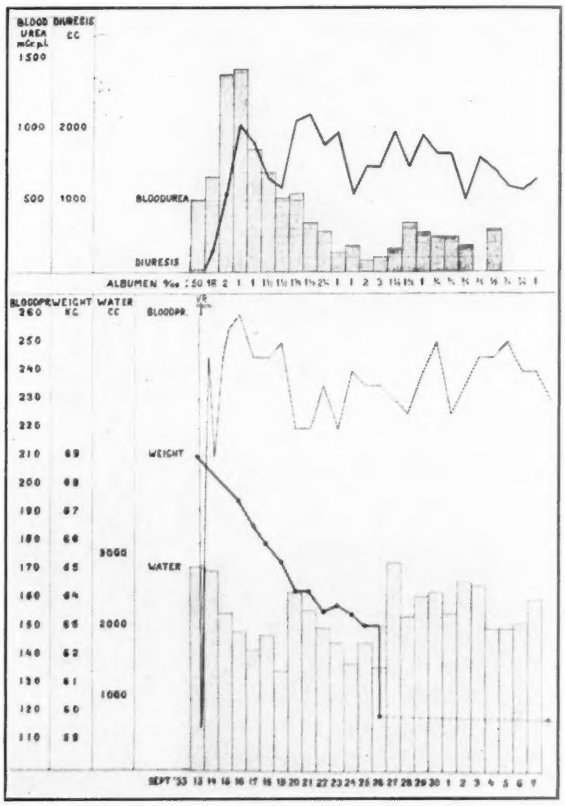

Fig. 4.

free diet, or rather a diet poor in salt, though not on account of the salt itself, but to enable his patients to refrain from drinking. Moreover they attached great value to limiting the fats and albumin.

My patients, on the contrary, may have anything they like, except milk, but all without salt and with an additional liter or two of water. Table I shows most clearly that this water has no ill effects. On the contrary, it is beneficial; severe cases of toxemia even with anuria can be cured thereby, as the following example will show.

Fig. 4 shows the quantities of water, the diuresis, the weight and quantity of salt excreted in a primipara, who on admission had extensive edema, a high blood

pressure (230), marked albuminuria (50 per cent), vomiting, and epigastric pains. To prevent the outbreak of convulsions a vena section of 500 gm. is performed and morphine given. The diuresis had almost stopped. The patient is given much water, no salt. The diuresis increases first slowly, then more rapidly, whereupon the weight decreases and the edema disappears, but the blood pressure remains high. No convulsions occur. You will observe the great quantities of water used, and yet the deep fall of the weight. In the first days the urea content of the blood augmented from 600 until about 1500.

It is my firm belief, therefore, that there can be no longer any doubt that the salt is the culprit and that it is to blame not merely for the eclampsia but partly also for the toxemia.

It would be well if the women were to be forbidden the use of salt in the second half of their pregnancy. There would then be far fewer cases of serious toxemia, and it would practically put an end to eclampsia.

Such a measure, however, as was remarked above, is not required, because we are able to detect the danger of eclampsia in time, not only in the hospitals but also in the ordinary practice, which implies that the prophylaxis of eclampsia has become simply a matter of organization, in other words, of prenatal care.

And herewith I come to the practical part of the prophylaxis of eclampsia. This is not such a simple question as it appears at the first glance, for it demands a vast amount of work which, and that is the drawback to all prophylaxis, is not adequately appreciated.

Many women, in my department too, evade the control, and many others do not keep strictly to the prescribed orders. The consequence is that the results are not what they might be. But if we are not disheartened by an occasional case of eclampsia, but after each fresh case take new and more stringent measures, the results will be by no means unsatisfactory, as is seen in my Obstetrical Department at Utrecht. You will allow me, therefore, to give you a short survey of this work, with annexed prenatal care together with the results that have been attained in the last ten years.

In Utrecht, a town with ± 175,000 inhabitants, about 3,000 children are born every year, of whom ± 2,000 come under my department.

Of these about 250 are admitted in the Clinic, the others are delivered at home with the aid of students, under control of one of the assistant doctors.

When the expectant mother reports herself, which as a rule is in the seventh month, she is registered and weighed, the blood pressure measured, the urine examined, the size of the uterus and the position of the child determined and, if necessary, the pelvis is examined internally. When there are no anomalies, the women are bidden to return every fortnight for control; in other cases earlier, and, if need be, they are treated at home, or admitted to the Clinic.

During the first years they were seen on an average of 3 times; in the last year on an average of 5 times. This shows the growing confidence of the public.

About 25 per cent were put upon a salt-free diet, a large quantity.

A specification of this figure for the year 1936 follows here:

FREQUENCY OF SALT-FREE DIET

Utrecht:		
Number of inhabitants	±175,000	
Number of births, 1936	3,335	= 19%
Department of University:		
Number of births	2,149	
Clinical confinements	256	
Home confinements	1,873	
Salt-free diet	562	= 26.1%
Indications:		
Edema only	251	
Edema + hypertension	124	
Edema + hypertension + albuminuria	23	
Hypertension only	133	
Hypertension + albuminuria	14	
Albuminuria only	6	
Prophylaxis	10	
Epilepsy	1	
	562	

It should be noted that many women often exhibit hypertension on the first examination, a symptom, which is purely psychogenic. To make sure as far as possible that the diet is being strictly kept, the women get a diet-list and at their next visit, a week later or even earlier, they must bring a urine specimen, which is then examined for the salt percentage, as I have already described.

The delivery, whether in or outside the Clinic, is, as a rule, strictly expectant, i.e. within normal limits it is allowed to proceed without interference; and without narcotics. The total number of registered confinements in these ten years was about 20,000, clinical births included.

Forty-five women died after registration, 10 before birth, 35 after birth. There were 27 puerperal deaths:

Sepsis	9
Embolism	5
Placenta previa	6
Premature separation of the placenta	2
Hemorrhage postpartum	3
Apoplexia	1
Anesthesia	1

Nonpuerperal deaths—10

Tuberculosis	6
Pneumonia	4
Hematemesis	1
Appendicitis	1
Coma diabeticum	1
Paralysis cordis	2
Full-term ectopic pregnancy (laparotomy)	1
Unknown cause, antepartum	2

There were 27 puerperal deaths, but, what is of the greatest importance, *not one patient died of eclampsia*, or of toxemia.

Yet 21 of the 20,000 women did get eclampsia, and it is essential to inquire further into these cases.

A. It appears, then, that of these 21 women 9 are primiparas, and 12 multiparas, which is a different proportion to the usual one. There is little doubt that this will be because the primiparas submit to be controlled much better than do the multiparas.

B. Two women had eclampsia in whom shortly before not a single anomaly was be found. In our ward practice, too, we met with 2 such cases.

Three times the eclampsia occurred the day after the woman was registered: once in the twenty-fifth week, once in the thirty-third week, and once in the thirty-ninth week, all three shortly after being admitted to the Clinic, one almost immediately after admission, while still in the bathroom.

These women were thus too late.

Three women failed to return after having been prescribed a diet. Eleven had been controlled regularly, but had not adhered strictly to the diet, and,

Twice the necessary prescriptions were not given, notwithstanding serious anomalies.

C. Further it appeared, that the 2 women, who had evinced no anomalies, had 5 and 8 attacks.

The women who failed to return had on an average of 5 attacks.

The women who had not kept their diet strictly, had only 3 to 5 attacks. All these women have recovered, but on the other hand by the same treatment, from 60 other women, who were admitted with eclampsia, 13 died. It is evident, that the prognosis of eclampsia does not depend only upon the manner of treatment, conservative or active, but in a high degree upon the use of more or less salt in the preceding days. This would perhaps explain the great difference in the mortality in different countries, especially the beautiful results of Stroganoff, whose mortality, in Leningrad is only 2.9 per cent, a mortality which, I think, nobody else can boast. To make sure it is necessary to know the frequency and severity of eclampsia in the different countries in relation to the welfare.

As you know the frequency of eclampsia in Germany during the war was very low, and also in Rotterdam, the frequency had sunk in 1918 to almost a third.

In my opinion this is to a great degree due to the small use of salt as an immediate consequence of the shortage of food."

In my report of geographic eclampsia for the International Gynaecological Congress in Amsterdam, 1938, I especially will pay attention to this undoubtedly important point.

When indeed the salt has the signification which I believe it has, it merely depends upon the organization of the prenatal care and in particular on the cooperation of the public how many cases of eclampsia still will occur.

In Holland, great attention has been paid to the prenatal care for more than forty years. As can be readily understood, the results are not equally favorable everywhere.

Of 175,000 births, there were 64 deaths from eclampsia and albuminuria in 1934, and in 1935, 75.

From figures furnished me by the Statistical Bureau, I find that of these 75, 54 died from eclampsia, namely one in about 3,000 deliveries.

This low mortality is especially due to the help of the midwives in prenatal care. This they have allowed by law to carry on for some years now. For more than forty years the probationer-midwives at the Training Schools, have been taught to examine the urine, every fortnight, and for twenty years they have also been instructed to determine the blood pressure, and many do this conscientiously in their practice. Further, a vigorous propaganda for prenatal care has been carried on, verbally and in writing, and in particular at the Classes for Mothers, which were instituted in 1912, and have been given for many years now in every town and every village by the "Green Cross" organization.

Besides the individual prenatal care, which extends to the Lying-In Hospitals and Midwifery Wards of the Hospitals in the cities, the need of organization of the prenatal care has made itself felt in the country especially, and an Association has been formed for prenatal care as a subdepartment of the Netherlands Association for Infant Welfare, with the support and cooperation of the State.

The Association organizes and controls the prenatal care over the whole country. The leading principle is, that every woman is controlled as much as possible by her own doctor or midwife.

This Association is drawing the reins tighter and tighter. And this is necessary, for still there are many women who evade our control. But fortunately we are so far that there is now no doctor or midwife who would not be ashamed to have any of their patients develop eclampsia.

We have confidence, therefore, that the figure for eclampsia may still be reduced, and this will be due in large measure to our blood pressure control, which hardly ever fails to give timely warning, and to the salt-free diet, which enables us with almost complete certainty to ward off the impending danger.

These two facts in my opinion dominate the prevention of eclampsia, and I venture to recommend them to your careful attention.

DISCUSSION

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—Dr. De Snoo has stressed the importance of chloride retention, hypertension, the danger of fits because of their

associated vascular spasm, and the normal kidney. He also postulates a cramp center. He states very definitely and proves with statistics that they have been unable to prevent toxemia but can prevent eclampsia in the majority of patients. I agree with him in most of these points but differ in the importance which he attributes to the fit per se and the degree of hypertension.

It has been demonstrated experimentally that if the brain is first dried out by means of a hypertonic solution it will require a larger amount of the stimulating substance, for example, absinthe, to produce convulsions than with the normal brain. I believe that one can account for the convulsions of true eclampsia on physicochemical changes between the blood and the fluid in the tissue spaces.*† Where the patient has gained excessively in weight but shows no edema, convulsions rarely occur. Occasionally these patients, within a period of a few hours, will show evidence of very marked pitting edema. In other words, the water which has been bound has for some reason become free, and it is in these patients that convulsions are most likely to occur and also symptoms of cardiac failure as evidenced by pulmonary edema, cyanosis, and tachycardia.

Patients with essential hypertension may also have convulsions which are presumably due to changes in the arterioles and capillaries. These fits, if they occur in the pregnant woman, cannot be differentiated from those of eclampsia. It seems to me that some of the apparent contradictory results with various therapeutic procedures for treating eclampsia can be attributed to these two different etiologic causes. True eclampsia due to the pregnancy and characterized by a wet brain, marked alterations in blood and plasma volume and other abnormal physiologic changes is not so amenable to treatment and is cured as a rule only by relatively early delivery.

The convulsions due to a hypertensive encephalopathy are not materially affected by the pregnancy, although the latter condition may favor their occurrence and are readily controlled by hypnotics. Since the pregnancy is not the cause, early delivery is not so important. We do not know what eclampsia is and, therefore, cannot at present differentiate these two conditions during the acute attack but believe such a possibility should be kept in mind.

We reported before this Society in 1929 data on the retention and excretion of sodium chloride by the preeclamptic and eclamptic patient. In 25 patients with eclampsia,‡§ the chloride concentration of the urine on admission ranged from 0.002 to 0.41 gm. per cent, with an average of 0.185. Data from two eclamptic patients who were discussed in the previous report are presented in Table I. W. P. showed almost no chloride excretion before delivery, although on a salt-poor diet. The maximum diuresis in both patients occurred when the serum protein concentrations were at their minimum.

TABLE I

PATIENT	TIME	WT. LOSS IN 3 WK. PERIOD KILO	SERUM PROTEIN GM. %	URINE: AVERAGE PER 24 HOURS			
				NO. OF DAYS	VOLUME C.C.	NaCl	
						GM.	CONC. GM. %
W. P.	Antepartum		5.6	2	1,000	0.12	0.008
	Postpartum	20	4.3	3	4,700	13.6	0.31
M. W.	Antepartum		6.8				
	Postpartum	50	4.9	3	4,816	20.77	0.43

Dieckmann, Wm. J.: AM. J. OBST. & GYNEC. **32**: 927, 1936.
†*Idem. Ibid.* **26**: 543, 1933.
‡*Idem.* AM. J. OBST. & GYNEC. **29**: 472, 1935.
§*Schwarz, O. H., and Dieckmann, Wm. J.: Ibid.* **18**: 515, 1929.

TABLE II. C. W. (THIRTY-EIGHT YEARS OLD, GRAVIDA VIII, PARA VII, TWIN PREGNANCY AT TERM, POLYHYDRAMNIOS)

	URINE: AVERAGE PER 24 HOURS			B. P. MM. HG.	WT. KILO	SERUM PROTEIN GM. %
	VOLUME C.C.	NaCl				
		GM.	GM. %			
2/14				160/ 60	88	
2/28				114/ 60	89	Admitted to the hospital
4/18	140	1.0	0.72	172/ 95	109	5.3
4/19	400	2.7	0.67	215/118		Delivery
5 days	4,450	7.4	0.18	185/105		4.8
11 days	3,036	19.8	0.66	160/ 95		5.5
3 days	2,600	2.6	0.10	145/ 90		
5/1				135/ 90	68	6.9
6/6				125/ 75	70	6.6

Table II lists essential data from a patient who had no convulsions. The close relationship between weight gain, edema, hypertension, and proteinuria is evident. The marked excretion of chloride after delivery with the patient on a salt-poor diet is indicative of the retention which had occurred previously. As the edema decreased, the blood pressure returned to normal and other abnormal symptoms and signs disappeared. We have noted that improvement does not occur before delivery and not always then, unless the chloride intake is reduced to such a degree and the restriction maintained long enough in order that the total excretion in the urine is less than 3.0 gm. as NaCl.

I have always looked upon the convulsion as being only one sign in the disease, eclampsia, and have felt in general that, as long as the patient is able to respond to the abnormal condition by having convulsions, the prognosis is more favorable than if coma, hyperpyrexia, anuria, etc., develop without convulsions.

If Dr. De Snoo is correct in attributing the importance which he does to the hypertension and a theoretical cramp center, then the higher the blood pressure, the more serious the eclampsia. This has not been our experience. I prefer an eclamptic patient with a blood pressure of 200/170 to one with a blood pressure of 160/130. One of our fatal cases was a patient who had a maximum systolic pressure of 128.

At the Chicago Lying-In Hospital in a period of five years and seven months, during which there were 14,864 deliveries, 52 patients had eclampsia, an incidence of 0.346 per cent. Thirty-two of these eclampsias occurred before delivery and the remainder occurred postpartum.

TABLE III

	PRENATAL SUPERVISION		FAULT		
	CARE	NO CARE	DOCTOR	PATIENT	NO ONE
Our clinic	23	6	18	10	1
Other clinics	4	2	4	2	
Private patients	13	4	16	1	
Total	40	12	38	13	1

Prenatal Care.—In Table III, data are given as to the amount of prenatal care, and I have attempted to assign the fault of eclampsia to either doctor or patient with the result that in only one case was no one found responsible for the eclampsia and the resultant death. Such reasoning is fallacious, because after the patient has had eclampsia, it is easy to state that some other procedure might have prevented the disease or saved her life. It is interesting that 38 patients were seen one week or more before the delivery, and the doctor was apparently at fault in not preventing eclampsia in these patients. It is also interesting that the first symptom

of toxemia, either hypertension, albuminuria, edema, or excessive gain in weight, was first noted at 33.5 weeks' gestation, and the eclampsia occurred at thirty-seven weeks. On examining the prenatal records of the 23 patients seen in our clinic, who subsequently had eclampsia, it was quite obvious that the internes did not interpret abnormal findings properly. These patients had adequate prenatal care, but it was not intelligent prenatal care.

The toxemia clinic was started in January, 1932, and we have been seeing most of the patients with toxemia. To date no patient who was seen in that clinic has developed eclampsia. Considerable discussion has arisen in the literature in regard to the value of prenatal care. None of us who have had experience in obstetrics doubts its value, but in view of the fact that its value is being questioned, a few comments are of value. At the East End Maternity Hospital in London, whose records go back to 1884 and which had a death rate in the nineties of 1.9 per 1,000 live births, the rate now is 0.68. Furthermore, in the last 10,000 consecutive deliveries only one case of eclampsia occurred and she had had no prenatal care for a period of three weeks.

According to the English classification, 33 patients had mild eclampsia and 19 the severe type. When the patient has eclampsia, one must decide early as to the course of treatment and cannot wait until there have been twelve fits, coma, temperature of 103°, etc. We classify as severe any case in which *one* of the following occurs:

Temperature of 39° C. (102° F.)
Coma
More than 10 convulsions
Cardiovascular impairment (cyanosis, râles, low blood pressure)
Failure of "proper treatment" to
    check convulsions
    produce urinary output of 700 c.c. or more per twenty-four hours
    prevent onset or deepening of coma
    produce a blood dilution.

With this classification the figures were the same but 12 patients were transferred from one to the other class.

Termination of Pregnancy.—There were 10 cesarean sections and 6 vaginal hysterotomies and/or Dührssen's incisions. Thus our treatment of the condition is still rather active. At the old Chicago Lying-In 12 per cent of the cesarean sections were for eclampsia and toxemia. At the new Lying-In Daily gives 14.4 per cent for this group of patients.

Maternal Mortality.—Of the 3 patients who died one had had prenatal care. As is evident from the protocol, we did not attribute sufficient importance to the marked gain in weight. The other two patients had had no prenatal care, although one, who was in the hospital twenty-four hours before death, could probably have been saved if the pregnancy had been terminated shortly after admission.

Fetal Mortality.—There were 57 babies from the 52 pregnancies. Of these 12 were stillborn or died neonatally. Two mothers died undelivered. Thus 14, or 24.5 per cent, of the babies were lost. Of the total deaths 11, or 79 per cent, weighed less than 2,500 gm. One-half of all babies weighed less than 2,500 gm., and one-third less than 2,000 gm.

I have been collecting statistics on the geographic distribution of eclampsia and the other toxemias of pregnancy. The collective data (Table IV) for representative hospitals in the United States are of interest and suggest a number of questions. Why do the incidence and mortality in the hospitals vary? Is the eclampsia more severe in certain areas or do the doctors know less in these cities where the mortality is high?

TABLE IV

HOSPITAL DELIVERIES	NUMBER OF DELIVERIES	ECLAMPSIA		NONCONVULSIVE TOXEMIA	
		INCIDENCE	MORTALITY	INCIDENCE	MORTALITY
		% 1	%	%	% 1
Chicago Lying-In Hospital	13,735	0.36	6.0	7.28	0.30
Collective—U. S.	254,564	0.583	13.06 (194)	4.41	1.68 (156)
Collective Range—U. S.		0.6-7.2	0-50.00	0.2-29.6	0-13.0

The approximately equal number of deaths from eclampsia and nonconvulsive toxemia is also of interest. These figures indicate the need for more study of the latter group and earlier recognition of the criteria necessary for interruption of the pregnancy.

These questions can be answered if a sufficiently large number of patients can be studied and treated with the various "treatments." This presupposes cooperation between universities and hospitals. The initiative in such a plan for coordinating study of the toxemias of pregnancy should be by the special societies or by one of the large research foundations. The latter is preferable for many reasons.

Dr. De Snoo has mentioned the diet as a factor in the cause of eclampsia. I wish to call attention to our work on nonpregnant dogs.* These animals were fed meat and at the proper time interval were given placental extract intravenously. Over 50 per cent of the animals had hemorrhages and necrosis about the portal spaces of the liver and beneath the capsule. We suggest that this work indicates that protein, especially meat or fish, is contraindicated in patients with preeclampsia. It is probably not injurious to pregnant patients with essential hypertension.

In 12 patients, 5, or 40 per cent, gave a history of previous toxemia. Likewise, 5 out of 21, or 22 per cent, had toxemia in subsequent pregnancies. The number of cases is small because in a larger group of nonconvulsive toxemia we find a much greater incidence of toxemia after eclampsia.

The treatment† which we have been using has been described on several occasions and may be summarized as follows:

TREATMENT OF ECLAMPSIA

General: Constant observation. Retention catheter. The temperature, pulse and respiratory rate, blood pressure and urine volume should be determined every two hours until the patient is conscious. Oxygen is administered for cyanosis.

Convulsions: At least two of the following drugs are used: Magnesium sulphate: 10 c.c. of a 25 per cent solution, intramuscularly and 5 c.c. after every convulsion until controlled. Luminal-sodium: subcutaneously, 0.3 gm. (5 gr.), every eight to twelve hours. Morphine sulphate: ¼ gr. every hour until convulsions cease or respirations become 12 per minute. Chloral hydrate: 2 gm. (30 gr.) in 100 c.c. of starch water are given by rectum every six to twelve hours.

Elimination: Soapsuds enema.

Hypertension: Sedation, especially barbiturates and chloral hydrate.

Renal and Cerebral Symptoms: The intravenous injection of from 500 to 1,000 c.c. of a 20 per cent solution of glucose, 2 or 3 times daily given within forty to sixty minutes. Sufficient glucose is injected to insure a urinary volume of at least

*Dieckmann, Wm. J.: AM. J. OBST. & GYNEC. 18: 757, 1929.

†Idem: AM. J. OBST. & GYNEC. 33: 165, 1937.

30 c.c. per hour. Occasionally a 30 or 50 per cent solution in smaller amounts is necessary. Normal saline, Ringer's or bicarbonate solutions are *contraindicated.*

Pregnancy: If the patient is in labor, it may be hastened by rupture of the membranes or the use of a bag. If the patient is not in labor, we may, after a diuresis has been established, consider: (A) Induction of labor, as described above, or (B) cesarean section. This operation should only be performed if the case is of the severe type or if cephalopelvic disproportion exists. Local anesthesia should be used and the environment must be suitable.

Diet: Nothing is given by mouth until the patient is conscious. As soon as the stomach is emptying itself, 50 c.c. of a 10 per cent Karo syrup solution are injected through a nasal tube and increased 50 c.c. every hour up to the patient's tolerance (usually 200 c.c.) and continued until the patient is able to take water and fruit juices by mouth.

CONCLUSIONS

Prenatal care will not prevent nonconvulsive toxemia of pregnancy but it will, if the various abnormal symptoms and signs are intelligently interpreted, prevent the occurrence of eclampsia and severe preeclampsia.

The normal pregnant woman has a positive balance for water, sodium, and chloride. We do not know which is primary. In certain pregnant individuals the retention becomes abnormal and various symptoms and signs occur. A diet which contains so little sodium chloride that the twenty-four hour excretion in the urine is less than 3 gm. is efficacious in most patients in reducing the edema and preventing eclampsia.

A co-ordinated systematic study of the toxemias of pregnancy should be made under the auspices of the special societies or one of the research foundations.

DR. JOHN R. FRASER, MONTREAL, QUE.—In our clinic in Montreal from 1927 to the present time in about 20,000 cases there have been 104 eclamptic cases with 10 maternal and 35 fetal deaths. In that time the policy of the clinic has been to adopt a decidedly palliative plan of treatment. Of those 104 cases 69 were primiparous women with an average age of twenty-four and thirty-five multiparous with an average age of thirty-one. The average number of convulsions in the group was 3.5. The termination in 62 cases was by spontaneous delivery; in 42 by induction. Of the 42 induced cases, which obviously were severe, there was medical induction in 7, rupture of membranes in 20 and bag induction in 15. Where the labor was terminated it was done with the least possible disturbance, low forceps in 19, midforceps in 10, breech extraction in 4, and cesarean section in 3 cases.

Now if we contrast that series of cases with the period when a much more active, surgical treatment of eclampsia was in vogue, we see a very different picture. There were 129 cases when accouchement forcé was more in use. In 69 cases there was a mortality of 28 per cent, a fetal mortality of 62 per cent. Abdominal cesarean section was done in 13 cases, with 39 per cent maternal mortality and 15 per cent fetal mortality. Where palliative measures were adopted, there was a maternal death rate of only 2.3 per cent. It would appear from this small series of cases that the pendulum in our clinic has swung in the same direction that it has all over this continent and abroad. We are adopting gradually the general principle of the plan laid down by Stroganoff.

Unquestionably cesarean section is required in certain cases and under certain conditions, but in our view cesarean section has only a limited place in the treatment of eclampsia. We feel that eclampsia calls for a more palliative policy which would be governed by three things, namely moderate narcosis, moderate elimination, delivery at as early a date as is consistent with the condition of the individual patient.

To discuss briefly the question of prevention, it is true that one is impressed with the experience of Professor De Snoo with a salt-free diet, and with recent observations based on hormone assays. Yet as practical obstetricians it would appear to us that what is required, is first quick recognition of the very early forms of toxemia and immediate institution of treatment. Failing prompt recovery we must rid the uterus of its contents. There is also an urgent demand for a much more prompt and radical method of dealing with the chronic nephritis cases.

DR. OTTO SCHWARZ, ST. LOUIS, MO. (Read by the President).—In 1929 Schwarz and Dieckmann reporting from Washington University on the treatment of eclampsia stressed:

1. The importance of conservative management.

2. The relationship between blood concentration and unfavorable clinical signs and symptoms and vice versa the clinical improvement associated with blood hydration.

3. The advantage of grouping cases as mild or severe and establishing the fact that mild cases gave better end-results when treated conservatively, whereas severe cases gave better end-results if handled actively.

Since that report was made, or in the last seven years (1930 to 1936 inclusive) it has been the policy in this clinic to continue to emphasize conservative management of eclampsia, but to recognize also that certain fulminating cases (severe eclampsia) must be treated actively as they are in too critical a condition to survive a period of expectant waiting. Hence the following outline of treatment:

A. CONSERVATIVE MANAGEMENT

1. *Sedation.*—10 c.c. of 25 per cent $MgSO_4$ given intramuscularly (gluteus) immediately after the first convulsion. Repeat in 5 c.c. amounts after each succeeding convulsion until controlled. If patient is in coma or not having convulsions no intramuscular magnesium sulphate is given as it is considered simply a sedative.

2. *Elimination.*—Colonic irrigation using soapsuds or plain water until the return is clear. Gastric lavage using normal saline or a weak sodium bicarbonate solution until the return is clear. Before removing the stomach tube, introduce 60 c.c. of 50 per cent magnesium sulphate into the stomach, using retention catheter for accurate determination of urinary output.

3. *Dilution.*—1,000 c.c. of 20 per cent glucose intravenously, given in forty to sixty minutes, twice or three times daily, depending on response of patient. Higher concentrations of glucose (30 per cent or 50 per cent) may be necessary if diuresis is not established. This is particularly true if much edema is present. Usually 300 to 400 c.c. of the 30 per cent or 100 to 200 c.c. of the 50 per cent glucose is given at one injection. Careful check on heart and lungs *before* injection of any volume of intravenous glucose in excess of 300 c.c.

4. *Nutrition.*—Usually after twenty-four hours the patient will tolerate food and is given a diet consisting of fruit and fruit juices. Under no circumstances should any food or fluid be injected into the stomach if the patient is comatose.

5. Vaginal instillations of recently prepared 1 per cent neutral acriflavine in glycerin, 8 c.c. twice daily. This is in anticipation of any necessary manipulation from below.

To this point the treatment is entirely conservative with sedation, elimination and blood hydration being stressed. What the management will be beyond this point is entirely dependent on the response to the above measures. Usually twelve to twenty-four hours is sufficient time to show whether the patient can continue on a conservative regime with reasonable hope for a favorable outcome or whether active

intervention will be necessary. If there is no improvement or if the condition grows worse, then the patient must be considered a severe case and active obstetric interference is indicated.

B. ACTIVE MANAGEMENT

This means delivery of the patient.

(1) *Examination.*—To determine various factors pertinent to actual delivery: e.g., condition and parity of the mother, size of pelvis, size of baby, presence or absence of labor and the *condition of the cervix.*

2. *Delivery.*—(a) Patient in labor, general condition fair, cervix short and dilating. (1) Rupture of membranes, (2) insertion of bag, (3) oxytocic, and (4) forceps. (b) Patient not in labor, cervix firm, closed. Abdominal cesarean section *under local anesthesia.*

Postpartum Care.—Continue intravenous glucose to keep up satisfactory urinary output. Continue elimination from bowels.

If glucose even in 30 per cent to 50 per cent concentration fails to produce diuresis, phlebotomy 500 to 600 c.c. may be resorted to, but if done a donor should be ready, or the blood should be citrated as withdrawn from the patient.

In general *no* saline, Ringer's or bicarbonate solutions are to be given. Ninety cubic centimeters of 50 per cent magnesium sulphate, as a rectal tap six or eight hours if necessary, to decrease intracranial pressure if headache, convulsions or coma develop. If patient is very restless phenobarbital or sodium amytal by hypodermic is to be preferred to morphine.

If acidosis develops treat with sodium lactate solution: one part of a molecular solution of sodium lactate diluted with an equal or greater volume of 20 per cent glucose solution or distilled water (not Ringer's or saline for eclamptics) may be given intravenously in 300 to 600 c.c. amounts. If alkalosis develops treat with dilute hydrochloric acid, 1 to 5 c.c. dilute HCl being given in a small amount of milk or fruit juice every four hours. As an emergency treatment of alkalosis, calcium chloride may be given intravenously (25 mg. per kg. of bodyweight, or 0.5 c.c. of a 5 per cent solution per kg. of body weight). Do not give calcium chloride subcutaneously, on account of the possibility of slough. In either acidosis or alkalosis therapy the safest way to check the results of the therapy is to make repeated CO_2 and pH determinations on the blood.

In the seven-year period, 1930 to 1936 inclusive, 217 cases of preeclampsia were observed in the Washington University prenatal clinic. Of this group 26 or 11.9 per cent developed eclampsia. Of the 26 who developed eclampsia 2 or 7.6 per cent died. This mortality figure refers only to those patients receiving their prenatal and hospital care at Washington University.

In the same seven-year period four additional patients died of eclampsia on the Maternity Ward Service. Each of these latter 4 patients was admitted to the ward as an emergency without having had any prenatal care. Some idea of their critical condition when first seen may be appreciated from the fact that the average period of hospitalization for the four patients, from time of admission to time of death was 2.6 days. It is not necessary to comment further on these figures and the very important relationship between prenatal care and the incidence and clinical course of eclampsia that they imply.

The discussion of Professor De Snoo's paper was to include prevention and treatment of eclampsia. As regards treatment much is being advocated today that is not of universal approval. (One need probably look no further than the comments of those discussing this particular paper in order to find very important differences of

opinion as to what is and what is not proper in the treatment of eclampsia.) This unfortunate state of affairs simply bears witness to the fact that no specific or entirely satisfactory treatment for eclampsia has yet been found. As regards prevention, the guest speaker's presentation pleads eloquently the cause of prenatal care. We at Washington University are forced to agree with Professor De Snoo that, in the light of our past experience, far more ultimate good in the prevention of death from eclampsia will result from efficient prophylaxis in the form of adequate prenatal care than could possibly be accomplished by the universal application of any one of the various current systems of treatment, once the eclamptic state has developed.

DR. H. J. STANDER, NEW YORK, N. Y.—I have nothing to say with regard to the etiology of eclampsia as I know nothing about it. I may say, however, that we have put no emphasis upon salt-free diet. We have come to a point of view in which we place no importance on the diet of eclamptic patients, but in spite of that our results are fairly similar to Dr. De Snoo's.

We have approximately the same number of cases that Dr. De Snoo referred to, so that our figures are comparable to those presented. The incidence of eclampsia in our clinic is 1 in 555 pregnancies, while that of preeclampsia is 1 in 119 pregnancies, giving an incidence for the whole disease entity "Eclampsia—Preeclampsia" of about one in every hundred deliveries in the Lying-In Hospital (Table I). This disease constitutes about 12 per cent of all toxemias, including the nephritides (Table II).

TABLE I. INCIDENCE OF ECLAMPSIA AND PREECLAMPSIA IN 17,201 PREGNANCIES

	NO. OF CASES	INCIDENCE
Eclampsia	31	0.18% or 1 in 555 pregnancies
Preeclampsia	145	0.84% or 1 in 119 pregnancies

TABLE II. INCIDENCE OF TOXEMIA (INCLUDING NEPHRITIS) IN 17,201 PREGNANCIES

	NO. OF CASES	INCIDENCE
All types	1448	8.4% or 1 in 11.9 pregnancies
Eclampsia and pre-eclampsia	176	1.02% or 1 in 98 pregnancies or 12.1% of all toxemias

TABLE III. VARIOUS TYPES OF ECLAMPSIA

TYPE	NO. OF CASES	PERCENTAGE
Antepartum	7	22.58
Intrapartum	13	41.94
Postpartum	10	32.26
Intercurrent	1	3.22
Total	31	100.00

TABLE IV. TYPE OF DELIVERY IN ECLAMPTIC AND PREECLAMPTIC PATIENTS

TYPE	ECLAMPSIA		PREECLAMPSIA	
	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Spontaneous deliveries	11	36.67	74	51.03
Total operative deliveries:	19	63.33	71	48.97
Forceps, breech, etc.	10		44	
Cesarean section	2		16	
Induction	7		11	

Intrapartum eclampsia appears to be twice as common as antepartum (Table III), but this is probably not so, as many cases of intrapartum eclampsia undoubtedly are actually antepartum eclamptics, in whom labor was brought on by the eclampsia. The three types, ante-, intra-, and postpartum eclampsia, are probably equally frequent, while the intercurrent form is very rare.

A study of Table IV shows that spontaneous delivery occurred in over one-third of the eclamptic, and over one-half of the preeclamptic patients. Cesarean section was performed in 16, or 11 per cent, of the 145 preeclamptic patients, and in only 6.7 per cent of those who developed convulsions.

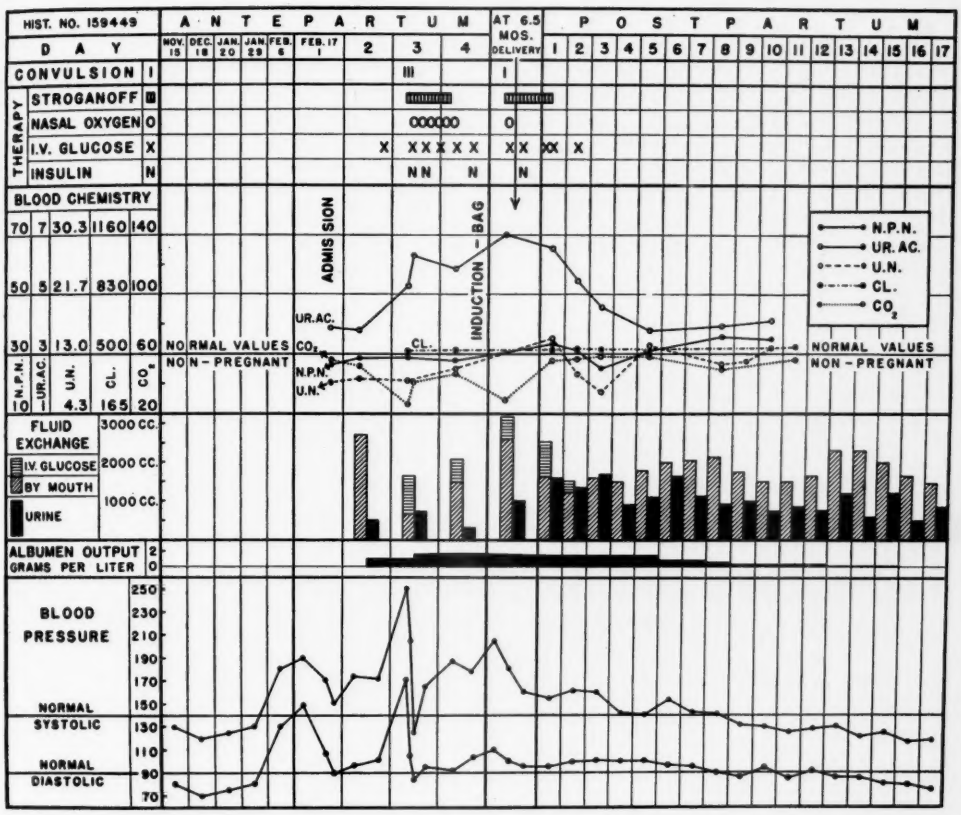

Chart 1.—Effects of therapy on various physical and chemical findings in a case of eclampsia.

Our treatment in eclampsia is conservative as shown in Table V. Over half of all our eclamptic as well as preeclamptic patients had conservative treatment only. In 40 per cent of the eclamptic and 38.6 per cent of the preeclamptic patients, the conservative treatment was supplemented with induction of labor (bag, bougie, or medical).

Our results from the time we opened the new Lying-In Hospital, Sept. 1, 1932, up to May 15, 1937, are presented in Table VI. During this period we treated 32 eclamptic and 145 preeclamptic patients, with no maternal mortality and with an infantile mortality of 25 per cent in eclampsia and 11 per cent in preeclampsia.

As we constantly utilize repeated blood chemical studies in the treatment of eclampsia, Chart 1 has been constructed to portray the variations in the chemical

findings and the effect on these of the appropriate treatment, such as anti-acidosis therapy, diuresis by concentrated glucose and sedation.

It is quite possible that Dr. De Snoo is correct in his assumption that salt plays a part in the production of eclampsia. I believe that some eclamptic patients die from a marked acidosis that develops very rapidly, and if you follow the blood chemistry, you can prevent that acidosis. The patients die from three to five days later from marked liver destruction and the only way to treat that is by glucose therapy. A third of them die from complications other than the straight eclampsia, such as lung complications. I also believe that the effects on the kidney are secondary and not the direct effect of the eclampsia.

TABLE V. TREATMENT IN ECLAMPSIA AND PREECLAMPSIA

TYPE OF TREATMENT	ECLAMPSIA		PREECLAMPSIA	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
Conservative	16	53.3	73	50.4
Conservative treatment followed by induction of labor	12	40.0	56	38.6
Bag	3	10.0	8	5.5
Bougie	5	16.7	9	6.2
Medical induction	4	13.3	39	26.9
Conservative treatment followed by cesarean section	2	6.7	16	11.0
Total	30	100.0	145	100.0

TABLE VI. MATERNAL AND INFANTILE MORTALITY IN 177 CASES OF ECLAMPSIA AND PREECLAMPSIA

	ECLAMPSIA			PREECLAMPSIA		
	NO. OF CASES	NO. OF DEATHS	INCIDENCE OF MORTALITY	NO. OF CASES	NO. OF DEATHS	INCIDENCE OF MORTALITY
Maternal	32	0	0	145	0	0
Infantile		8	25%		16	11%

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—Dr. De Snoo offers an interesting theory on the etiology of eclampsia which refers to the consequences of the large amount of salt, 15 to 20 gm. a day, ingested by the pregnant women of the Netherlands, and which is probably accounted for by the large amount of salted butter common in the daily diet of that country. An informal survey of the salt content of the diet of some 200 clinic and private patients in Philadelphia showed only two or three women who estimated that they ate more than two teaspoonfuls of salt a day. Whether or not these women made correct estimations of the salt content of their diet, it is a fact that a recent assay of the food in complete house diet of one day at the hospital of the University of Pennsylvania showed the salt content to be only 6 gm.

It is an unmistakable fact that toxemias of pregnancy which reach a convulsive stage are diminishing. In Pennsylvania in 1930, 208 deaths were certified as due to eclampsia; in 1935, 104. In Philadelphia in 1931 there were 41 eclamptic deaths, in 1936, 21. In the United States as a whole over the same period, the mortality rate from eclampsia fell from 16.3 to 10 per 10,000 live births.

In the different sections of the United States, we find evidence of wide variation in the incidence of convulsive toxemia. In some Southern states the proportion of toxemia and eclampsia deaths to the total maternal mortality reached 45

per cent, while in a midwestern city eclampsia is so rare that it has been found necessary to solicit such cases for educational purposes.

Where prenatal care reaches its highest degree of efficiency eclampsia falls to low statistical levels. The searching for and hospitalization of minor degrees of toxemia early in pregnancy will maintain admissions for toxemia of pregnancy at a fair level, but we will find marked diminution in the number of patients admitted in, or developing, a convulsive state. The hospital clinics in the city of Philadelphia from 1932 to 1934 carried 34,310 prenatal cases with 534 or 1.5 per cent developing some form of toxemia; 85 or 0.25 per cent developed eclampsia and of these 10 women died. It is evident therefore that the observation and treatment given these patients was responsible for the minimal death rate from eclampsia.

At the hospital of the University of Pennsylvania over a period of fifteen months in a total of 1,700 deliveries, there were 35 diagnosed as hypertensive pregnancy toxemia, 59 diagnosed as hypertensive vasculorenal diseases including nephritis. Thus we have an incidence of 5 per cent for admissions of various types of toxemia in late pregnancy. Four in the first group were regarded as preeclamptic and one emergency admission as postpartum eclampsia. This latter case represents the one mortality in the pregnancy toxemias series, and there was also one mortality in the hypertensive vasculorenal disease group. The present feeling of our clinic is that the division of "hypertensive pregnancy toxemia" and "vasculorenal hypertension" is artificial, and that future studies may show "toxemia" to be merely a phase in the development or course of underlying vascular disease.

Such cases are admitted from the prenatal clinic for study on the finding of albuminuria, hypertension, or excessive weight gain. The arbitrary limits we use are posted in the clinic and are taught to the students. Through the efforts of the Committee on Maternal Welfare of the Philadelphia County Medical Society similar standards for admission and study for potentially toxic patients have been widely adopted in the clinics of Philadelphia. At the Hospital of the University of Pennsylvania the routine studies on admissions include such clinical observations and laboratory examinations as are felt may throw light on the diagnosis and prognosis of the particular case of toxemia. The initial basic treatment of our cases consists in bed rest, house diet, and individually indicated measured intake of fluid, sedation and required intestinal elimination by salines.

The interruption of pregnancy in the various grades of toxemia is particularly individualized in the University of Pennsylvania Hospital. Each case is considered on its own merits. Briefly, increasing hypertension, systolic or diastolic, increasing albuminuria, and continuing signs of renal dysfunction are our main guides. Toxemic pregnancies are interrupted at the thirty-sixth week, or before, only in the presence of blood pressure above 160 systolic or 110 diastolic after continued bed rest of ten days or more, and in spite of the absence of other unfavorable findings.

Our treatment of the eclamptic attack would be conservative except for obstetric indications, and we would terminate pregnancy in such conditions only after recovery from the acute eclamptic attack. If recovery did not follow medical treatment of the acute eclamptic attack, we feel that obstetric treatment would not save the patient.

This conservative therapy is closely in line with the practice of the members of the Philadelphia Obstetrical Society which was reported some years ago by a survey of the treatment of eclampsia by the members of the Society. This showed a widespread tendency to conservatism with the resulting mortality of 5.4 per cent of all late toxemias and 21 per cent of all convulsive or comatose cases.

Until the etiologic factors of eclampsia have been discovered there can be no causal therapy for this symptom complex and a therapeutic negativism based on

the individual case will no doubt continue. The very best treatment of eclampsia lies in the prevention of the condition and this can be accomplished by efficient prenatal care.

DR. EDWIN F. DAILY, Director of Maternal and Child Health, Washington, D. C.—Newspapers, magazines, medical journals, and speakers throughout the entire country have for many years been focusing the attention of the people on the excessive maternal mortality in the United States. Most of this educational effort has been worth while and has resulted in a combined lay and professional realization of their joint responsibility in providing better care for pregnant women. In contrast there has been surprisingly little attention given to the constant lowering of our maternal mortality rate. Even if we only study the vital statistics for the years 1930 through 1935, years in which comparable, accurate, nation-wide figures are available, we find much to encourage us and considerable enlightenment regarding maternal mortality trends.

In this six-year interval the maternal mortality rate has been lowered 13.5 per cent; actually 2,292 fewer women died from all puerperal causes in 1935 than in 1930. Correcting this figure for lowering birth rates: if the 1930 maternal mortality rate had prevailed in 1935, there would have been 1,895 more maternal deaths in 1935.

Analyzing this steady and significant decrease in maternal mortality from 1930 through 1935 gives us some striking figures. The mortality rate for all puerperal sepsis decreased only 1.6 per cent. The mortality rate for puerperal hemorrhage decreased only 7.2 per cent. The mortality rate for puerperal albuminuria and eclampsia decreased 36.8 per cent. The marked decrease in deaths from eclampsia actually accounts for 54 per cent of the decrease in the number of puerperal deaths in 1935 compared to 1930.

In the urban areas of the United States 15.4 per cent of all puerperal deaths are assigned to albuminuria and eclampsia, while in rural areas 23.6 per cent are assigned to this cause.

Studying the percentage of all puerperal deaths which were assigned to puerperal albuminuria and eclampsia in the various states, we find that this percentage is highest in eight southern States. In fact, 55 per cent of all toxemia deaths in the United States occurred in the seventeen southern States in 1935, whereas only 37 per cent of the live births occurred in the same area. One of the most important factors in this distribution of deaths from albuminuria and eclampsia is indicated by the figures which show that, although 24 per cent of the deaths from toxemia in the United States are negro, yet only 12 per cent of the live births in the United States are negro.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—Two points in Dr. De Snoo's paper interested me very much, namely his reference to the importance of prenatal care and his subsequent statement that owing to State-wide attention to this subject they have prevailed upon women to come for examination at the seventh month. Most of us in this country would have an eclamptic convulsion ourselves if we did not succeed in getting prospective mothers to apply for prenatal care before the seventh month.

I believe, however, that we have somewhat exaggerated the value of prenatal care in obstetric practice and that we must give as great attention to intrapartum care in the future as to prenatal care. There is no question that so far as eclampsia is concerned, the better hygiene has resulted most favorably, but the good results do not seem to be apparent in any reduction of the puerperal deaths, particularly in those due to sepsis and hemorrhage.

DR. JAMES R. McCORD, ATLANTA, GEORGIA.—After seeing all of those blue spots on the chart presented by Dr. Daily, showing the large number of deaths from eclampsia in the South, particularly among the colored women, I must speak. The chart was interesting to me because Stander and Schwarz have always said that the disease is milder in the negro than in the white woman. This is not our experience.

In our present series we have had 164 consecutive cases of eclampsia in colored women with a total uncorrected mortality of 6.7 per cent. All these women had convulsions except one and the diagnosis of eclampsia in that woman was made at autopsy. Two cesarean sections were done in the series, both in 1928. A cesarean section has not been done in our clinic for eclampsia or preeclampsia since that time. Forceps deliveries were done 18 times. The remainder of the women delivered spontaneously.

We treat with one dose of morphine, magnesium sulphate, the dextrose solution. As soon as the convulsions are controlled labor is always induced. We do not see any use in tempting Providence further. We thoroughly believe in the conservative treatment of eclampsia.

PROFESSOR DE SNOO (closing).—That so many of my colleagues have participated in this discussion shows that eclampsia has the full attention of our profession here in America. I have seen this also in your literature. Your mortality figures in 1928 or 1929 showed that 5,000 women died from eclampsia. Last year the rate had diminished to less than 50 per cent. That is the best proof that the clinical care of your patients is very good.

Dr. Kosmak said that it is too late to have these women come in at the seventh month. He is entirely right and we endeavor to see those patients earlier wherever possible, particularly those whom we know have hypertension. But with the great mass of patients I think it is best to ask them to come at the seventh month, and then four or five times later because the last months are the most important. It is during the last months when eclampsia occurs and that is the reason we really begin with observation in the seventh month.

Feenders, H.: Hydatid Mole in a Fifty-Five-Year-Old Woman, Zentralbl. f. Gynäk. **60**: 2308, 1936.

Feenders states that many authors believe that hydatid moles occur more frequently in pregnancies of older women, although in reviewing the literature it may be seen that they occur relatively infrequently in women past fifty years of age.

The author reports the case of a fifty-five-year-old woman whose past history is essentially negative. She had six full term pregnancies, the last of which was a placenta previa, and four abortions. During the fifth month of the present pregnancy, the patient came to the clinic for vaginal bleeding. The diagnosis of climacteric bleeding was made. After no improvement with administration of ergot, a curettage was performed.

Peculiar grayish white pieces of tissue were obtained which on microscopic examination proved to be parts of placental tissue undergoing hydropic degeneration. The diagnosis of hydatid mole was made and the patient kept under close observation. Urine afterwards gave a strongly positive Aschheim-Zondek reaction. Five weeks later the uterus and the adnexa were removed, but the removed specimen showed no evidence of a chorionepithelioma.

The author feels that in similar cases the removal of uterus and adnexa is definitely indicated.

RICHARD E. SOMMA.

THE STILLBIRTH PROBLEM*

PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

DURING the past decade there has been a marked increase in the attention paid to maternal welfare and maternal mortality in the United States. More particularly the attention of the medical profession has been focused on their own communities as individual areas for study, so that at the present time there have been given to us reports of the circumstances regarding maternal deaths from widely separated portions of the United States. These studies have enabled us to draw conclusions regarding various problems of maternity care, and to note the special factors which seem to influence the varying proportion of deaths from one cause or another in different sections of the country.

As an analysis of maternal deaths is carried on in a community, certain associated or closely related problems or phases of maternity care begin to stand out prominently, and suggest themselves as separate topics for study and discussion. One of these problems is the amount and quality of prenatal care furnished by the facilities of the community. It is not difficult to assess the maternity care given to ward patients whose hospital records are available for study, on the other hand it is quite a different matter to attempt to evaluate the care given to pregnant women by private practitioners. A second problem of note is the extent of maternal morbidity following delivery, and the standards by which such maternity morbidity is established. A third might well concern itself with the loss of infants within a short time after birth, due for the most part to causes immediately connected with pregnancy and parturition. A fourth, but not necessarily a final problem, is that of the fetal mortality we term stillbirths, which I wish to discuss this evening.

When the statistical report of the first three years' study of maternal mortality in Philadelphia was prepared, the impressive, but not necessarily surprising, fact appeared that approximately eight times as many maternal mortalities occurred in connection with women who gave birth to dead fetuses as when a live baby was born. Some consideration of the circumstances surrounding stillbirths in Philadelphia has seemed necessary and such consideration would be appropriately timed, in view of the fact that the Children's Bureau of the Department of Labor is engaged in a nation wide study of this subject. It is recognized that in the last twenty years there has been a marked

*Read at a meeting of the Brooklyn Gynecological Society, March 5, 1937.

decrease in the death rate of infants under one year, and a smaller decrease in the death rate for the first two weeks of life. But there has been practically no change in the rate for stillbirths since vital statistics on this subject have been collected.

With this fact in mind the Children's Bureau has begun a study of stillbirths in order to obtain statistical information regarding fetal and maternal conditions associated with fetal mortality in hospitals, to try to make possible the development of a classification of causes of stillbirth (fetal and maternal), and to further the development of a special certificate for registration of stillbirths which will serve as a base for comparable statistics for the various states. This study has been stimulated by the recommendations of a Sub-Committee on Stillbirths of the American Public Health Association which for some years has endeavored to have a uniform definition adopted in order to provide for comparability of records and to promote completeness in registration and uniformity in the use of terms. To provide a widespread sampling of the statistics hospitals in different areas of the United States have been asked to cooperate in returning completed schedules for their stillbirths in which the twelve questions asked should develop many pertinent facts on stillbirths.

The standard certificate of stillbirth proposed by the above-mentioned committee carries on its face the usual questions of the standard birth certificate of the United States Birth Registration area together with the additional questions which came in use on the first of January, 1937, and which appear to deal more with the data of social security than medicine. On the figure showing the stillbirth study schedule the questions are checked which are also found on the face of the proposed new certificate of stillbirth. There is one exception in that the schedule specifies under operations, "breech extractions," while the certificate specifies, "breech delivery."

On the reverse of the proposed standard certificate of stillbirth are found two groups of causes for stillbirth: (A) those determined in the fetus such as infection, asphyxia, malformation, birth injuries and other causes, or unknown, all of which are subdivided: and (B) causes and conditions in the mother associated with the fetal death which are divided in sixteen groups in accord with the terminology of the International List of the Causes of Death. The eleventh group specifies the diseases of pregnancy and childbirth which are most largely responsible for or associated with stillbirths. It is recognized by the Sub-Committee on Stillbirths of the American Public Health Association that this list of causes of deaths from the standpoint of both the fetus and the mother is tentative, and will probably be subject to revision after the certificate has been studied experimentally in some selected lying-in hospitals and cities. The adoption of such a certificate should naturally be followed by a study by vital statisticians of the proportionate causes of stillbirth with a resulting influence, one feels, toward a reduction in the present number of stillbirths.

In 1931 Dr. Sterling, speaking for the United States Public Health Service, at a Child Congress in Peru, concluded that the stillbirth

problem in the United States was the most neglected one in the whole field of infant mortality, and that the stillbirth problem was one of greater magnitude than that of neonatal deaths. She stated that the stillbirth rate for the seven years for which such statistics had been kept formed practically a straight line. Since that time the birth registrations area of the United States has expanded to 100 per cent representation of the population. In 1922, with only 72 per cent of the population represented in this area, the stillbirth rate was 39 per thousand livebirths; in 1934, the last year for which figures are available, and at which time a 100 per cent population area was covered, the stillbirth rate was 36. The total number in 1922 was 70,010; in 1934, 78,503. The rates for the United States, over this period of years, and for the two states, New York and Pennsylvania are shown graphically in Fig. 1.

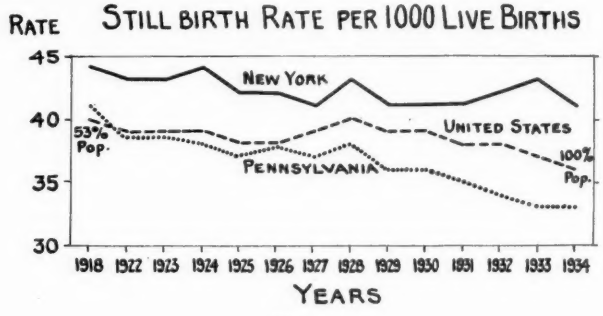

Fig. 1.

Since we have looked at the United States as a whole in regard to the rates and totals of stillbirths for a period of years it is well to examine into the rates shown by the various states for recent years, together with the definitions used for classification of stillbirths in the different component units of the United States. The basis of the study of the Children's Bureau was every fetus of twenty weeks' or more gestation born without signs of life, in the cooperating hospitals. The period of gestation and the definition of the stillbirth given for the schedule comes from rulings of statistical practice adopted by the American Public Health Association, namely, that a stillborn child is one which shows no evidence of life after complete birth (no breathing, no action of the heart, no voluntary action of any muscle). Birth is considered complete when the child is altogether, head, trunk, and limbs outside the body of the mother, even if the cord is uncut and the placenta still attached. The report of the Committee on Stillbirths of the American Public Health Association states that unless gestation has advanced to the fifth month, that is, 120 days, the product of the pregnancy need not be reported as a stillbirth.

In the accompanying outline map (Fig. 2) of the states, there are shown the varying periods of gestation at which they consider the product of conception stillborn as indicated by the upper figure, while the lower figure shows the stillbirth rate in each state for 1934, the last year for which figures are available. It will be seen that the majority of states accept the definition of the American Public Health Association that the pregnancy should have advanced to the fifth month, although there are other definitions which range from no definite rulings as to age, to any product of conception, to sixteen weeks, or twenty weeks, advanced to the fourth month, past four months, about the fifth month, about the sixth month and in, or past, or over the seventh month. Consequently, it is apparent how indefinite and conflicting studies of stillbirths from individual states would

Fig. 2.

become and how useless comparisons might be from the standpoint of obstetric practice. There is a wide variance in the definition of stillbirths from different states. Some consider the birth of a fetus whose heart is beating but which does not breathe, a stillbirth, while in other states the fact that the heart of the fetus beats after birth makes it a livebirth, and its death with the cessation of heart action a neonatal death.

The two most prominent authors from the investigative aspect of the problem of stillbirths in England may be quoted. Holland states, "a fetus becomes an infant, child, or baby as soon as it has breathed. The fetus dies when its heart ceases to beat." While Ballantyne, who may be considered the original investigator in antenatal pathology states that "the term stillbirth should be applied if a child is 'still' but with discoverable signs of life, such as beating heart, and the term dead births should be applied if life is actually extinct."

If we find varying definitions legal by states we find almost as wide variation in terminology and usage in medical studies of stillbirths and in hospital reports. A lack of uniformity or adherence to a common standard makes it difficult, if not impossible, to compare the results from one type of practice in a certain problem of obstetrics, as breech delivery, with the results achieved from another when the reports emanate from different clinics or cities. In most of the recent contributions on fetal mortality in medical literature one finds both a gross fetal mortality and a corrected fetal mortality set forth. Such corrections may be without apparent regard for the state definition of the stillbirth, and we find that individual authors correct their fetal mortality rate by subtracting variously all cases of macerated fetuses or congenital deformities or all prematures, which latter are listed arbitrarily according to length, weight, or period of gestation. Again

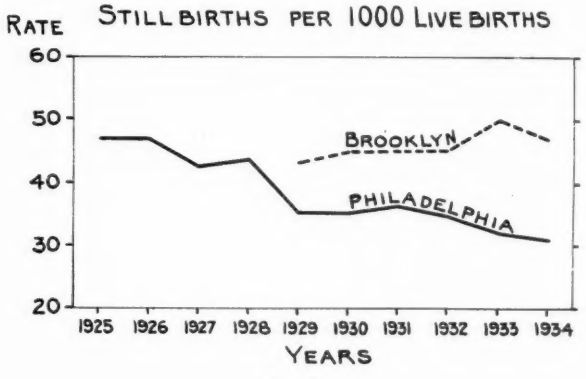

Fig. 3.

all twin pregnancies or emergency admissions have been eliminated or there have been subtracted all fetuses regarded as nonviable, and here again the definition of viability differs greatly. Some of these corrections do not appear justifiable.

The Pennsylvania definition of a stillbirth is a fetus which is past the fourth month, which does not show any sign of life without defining, however, whether the heart beat is a sign of life. In the state of New York any dead fetus advanced to the fifth month is regarded as a stillbirth, but the exception is made that this ruling is exclusive of New York City where any product of conception is requested to be registered. The stillbirth rates for Philadelphia and Brooklyn for the past few years as reported under the present definitions are shown in Fig. 3. It is probable, and very likely, that the higher stillbirth rate for Brooklyn is due to the disadvantage of this city in having to include any product of conception in its registrations of stillbirths. It is worthy of comment, however, aside from the definition that the rates of the two cities do not seem to have diminished appreciably in

recent years in spite of the attention which has been given to enlarge the amount and quality of antenatal care, and the increase of hospitalization for delivery in both cities.

A marked disparity in the stillbirth for the white and colored population in Philadelphia is shown in Fig. 4. The stillbirth in illegitimate pregnancies in inordinately high. Philadelphia is considered to have the largest colored population proportionately of any city north of the Mason and Dixon line. Since the maternal death rate among colored women in Philadelphia during our reported study was 7.2 as contrasted with an average of 6.2 in the white women it would seem that the excessive disparity between the stillbirth rates of the two races needed some study. The maternal mortality rate and the stillbirth in illegitimate

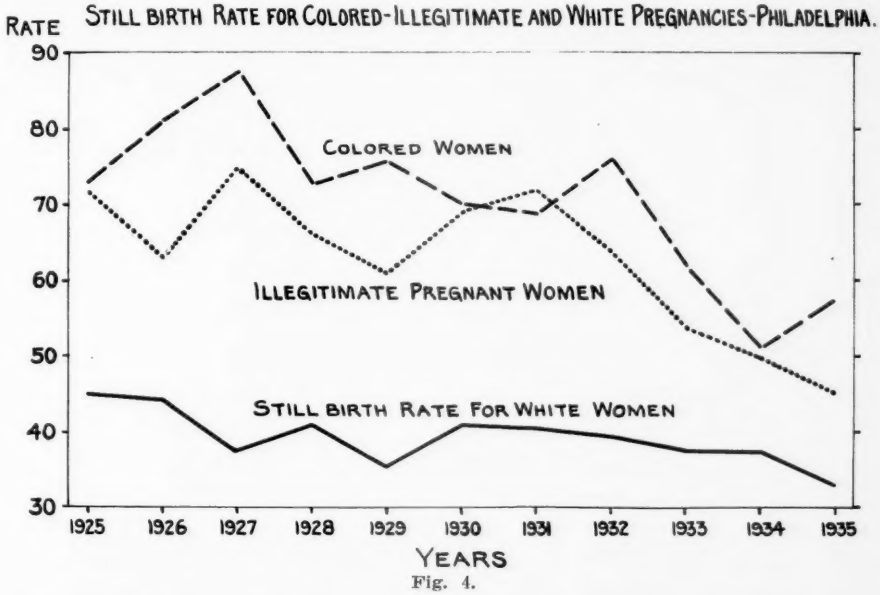

Fig. 4.

pregnancies were more nearly on a par, the maternal mortality rate being twenty, or over three times that of the legitimately pregnant women, while the illegitimate stillbirth rate was proportionately as high.

In contrast to the slight decrease in the stillbirth rate, it is a fact that the deaths from birth injuries in Philadelphia have shown a definite increase in the past few years. Whether or not this is due to a more careful and accurate reporting I do not know, but at any rate as hospitalization for delivery in Philadelphia has increased, the death rate of infants from birth injuries stepped up proportionately. During the period of our survey we found that the maternal mortality rate was almost eight times as great in women who gave birth to stillborn children as those delivered of live babies. As evidence of the effect of the continuing survey on maternal mortality in Philadelphia, we note that the death rate in women who gave birth to stillborn children

in the past two years of our survey was reduced 41 per cent, in the first year and 28 per cent in the second year.

It may be of interest that in 64 women in the first survey in Philadelphia who died as primiparas after stillbirth that there was an operative incidence of 84 per cent, that the three largest causes of death among those primiparas were sepsis in 18, toxemia in 20, and accidents of labor in 11. It is significant, too, that of 80 multiparous women who died after stillbirth one out of four had had previous stillbirths. Of the deaths in the first Philadelphia survey, in 98 cesarean section deaths there were 25 stillbirths, in 112 forceps deaths there were 42 stillbirths, in 65 versions deaths there were 34 stillbirths and in 36 multiple operation deaths there were 19 stillbirths.

To study a series of stillbirths in an institution with which I am connected I have applied the schedule of the Children's Bureau to the

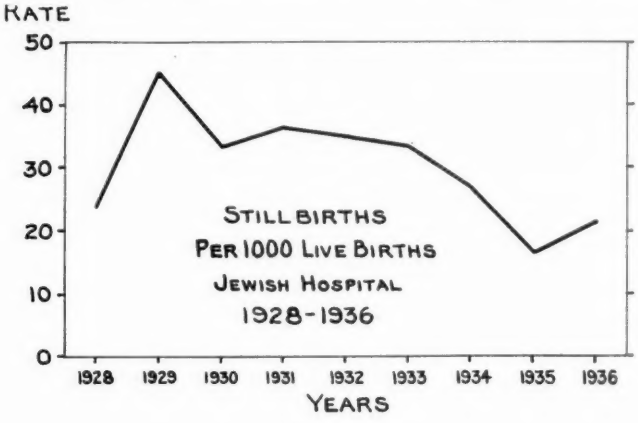

Fig. 5.

stillbirths which have occurred in the maternity division of the Jewish Hospital of Philadelphia, since it was opened, June 1, 1928 to Jan. 1, 1937. This has been conducted as an open service for ethical practitioners of the neighborhood, who cared to use the facilities of the maternity. It is only in the last three years that there has been any definite degree of supervision over, or regulation of the courtesy staff in their obstetric practice. At the present time the basic requirements of the American College of Surgeons for maternity divisions of hospitals are fairly effective in this institution although even yet there is some question at times of the qualifications or practices in the courtesy staff. I believe that the reduction of the stillbirth rate beginning 1934 is a result of a more stringent regulation of maternity practice adopted in the hospital. The stillbirth rate for the hospital, 28.8 in 7,895 deliveries, is shown in Fig. 5.

From this rather small series of 228 stillbirths probably basic deductions should not be made, and for the sake of comparison I will quote

occasionally, through the courtesy of Dr. Elizabeth Tandy, the findings regarding similar items from a preliminary analysis on the first 1,000 stillbirth schedules received at the Children's Bureau.

With respect to race, our series is almost uniformly white, for the hospital is situated in a residential section free of slum areas or black belts. The Bureau reports 81 per cent white and 19 per cent colored in 1,000 schedules. If my study was from the Philadelphia General Hospital service the figures would be almost the reverse of the Bureau figures for race. The age groups in our series, 33 per cent under twenty-five years, and 50 per cent from twenty-five to thirty-four years, were almost exactly those in the Bureau study.

There were 111 primiparas in our series, 48 per cent, as compared with 43 per cent in the first 1,000 schedules studied by the Bureau and 36 per cent of the total stillbirths registered in the United States in 1933; and 117 multiparas, 52 per cent. This grouping in our almost entirely white survey show our stillbirths were in young women, twenty-one to thirty and that this series is almost equally divided between primiparas and multiparas.

Since our tabulations were carried on the same uniform base as the Bureau study we may compare our figures as to the period of gestation (Table I).

TABLE I

	NUMBER	JEWISH HOSPITAL PER CENT	CHILDREN'S BUREAU PER CENT
20—27 weeks' gestation	57	25	18
28—35 weeks' gestation	53	23	31
35—40 weeks' gestation	113	49	46
Postmature	5	2	5

In defining a postmature fetus we have accepted the definition recently suggested by Adair to the Chicago Board of Health. His classification was requested for a study of the causes of infant mortality, and after a failure to find any sufficiently satisfactory or uniform criteria for the purpose.

A previable premature is:

1. From 400 to 1,000 gm. in weight.
2. From 22 to 28 weeks.
3. From 28 to 35 cm. long.

A viable premature is:

1. From 1,000 to 2,499 gm. in weight.
2. From 28 to 37 weeks.
3. From 35 to 47 cm. long.

A full-term infant is a baby:

1. From 2,500 to 4,499 gm. in weight.
2. From 38th to end of 43rd week.
3. From 47 to 54 cm. long.

A postmature infant is a baby:

1. More than 4,500 gm. in weight.
2. More than 43 weeks.
3. More than 54 cm. long.

Any infant that fulfills any two of the three criteria in any group shall be classified in that group.

LABOR

The time of fetal death with respect to labor was recorded in 93 per cent of the 228 records. In 78, or 34 per cent, death occurred before labor; in 136, or 59 per cent, death occurred during labor; while in 14 cases, or 7 per cent, the record was incomplete on this detail. In the Bureau study 56 per cent occurred prior to labor, during labor in 37 per cent, with 7 per cent, no labor or not recorded.

OPERATIONS

In this series of 228 stillbirths, 127 fetuses, 56 per cent, were delivered spontaneously and 101, 44 per cent, were delivered by operative procedure. Forceps, 49 per cent, was the most frequent type of operation of the operative procedures, followed by version, 20 per cent; breech extraction, 16 per cent; cesarean section, 10 per cent; craniotomy, 5 per cent. In the Bureau study 62 per cent were delivered spontaneously, and 38 per cent by operative procedure; divided into forceps, 35 per cent; breech, 25 per cent; version and extraction, 14 per cent; and cesarean section, 12 per cent; with the remaining percentage not stated.

The figures of one class almost reverse the findings of the schedule study by the Bureau; there it was noted that in 73 per cent of the stillbirths in which the fetus was delivered by operative procedure the fetal death had occurred prior to the operation. In our series fetal death occurred in 37 per cent before operation was performed. A conservative obstetrician can only speculate as to the indications leading to the high figure, 73 per cent, arrived at in the Bureau study.

In this series the fetal death occurred during 64 per cent of the operative procedure. Such cases demand an intensive introspection by a hospital staff. They should not be regarded as an unavoidable group, but rather as a remediable group. Either the time of operation, or its selection or performance must have been largely responsible for many of these fetal deaths. It seems difficult to believe that one-fourth of the high forceps operations and 41 per cent of the versions should have been associated with fetal death.

There were 25 surgical inductions of labor, 11 per cent of the series, most of these were done by the method of Slemons, with rupture of the membranes; a few labors were induced by bags or bougies. The majority of the indications were clear-cut, toxemia, nephritis, or medical conditions. The deaths were almost equally divided between the before labor group, and the during labor group. There were, four cases in which inductions were done at term, for which the record gives no clear indication where the fetus died during labor. It is to be surmised that these inductions represent the convenient group and the deaths serve to prove, even though a small percentage of the number of cases induced, that the induction for convenience is not without its dangers. In one of these cases 30 gr. of quinine were given during a period of four hours. The fetal death, the disappearance of the heart sounds, was noted one hour after the quinine was administered and before labor was established. This is the only instance in the many cases in which quinine was administered in medical or surgical induction where it was felt the drug might have played a part in the fetal death.

LABOR OVER TWENTY-FOUR HOURS

The influence of prolonged labor on stillbirth is well exhibited by the histories of the 47 cases where the labor exceeded twenty-four hours. Of these cases, half of which had operative delivery, 16 died of intracranial hemorrhage, 5 of asphyxia, and three of birth trauma. At the present time the hospital has a regulation calling for obligatory consultation at the end of twenty-four hours' labor. I am of the impression that this arbitrary time limit is too long, and that it should be eighteen hours or less, and that an arbitrary limit as to time will occasionally defeat the original purpose in allaying anxiety about the possible condition of a patient until serious cerebral trauma in the fetus may have occurred. Possibly an obligatory consultation for any marked alteration in the fetal heart rate would add in further protecting the fetus.

No note was made in this series as to the incidence of contracted pelvis. However, Peckham states that in a study of border line pelves with vaginal delivery the fetal mortality rate in labors of twenty-four hours or less was 7.19, a figure less than 1½ per cent above the rate pertaining to the general clinic mortality. In labors of thirty hours or more the fetal mortality rate rose to the appalling figure of 19.23 per cent gross.

MULTIPLE PREGNANCY

In the 7,895 deliveries from which this series of 228 stilibirths are drawn, there were 47 twin deliveries, an incidence of 0.6 per cent. Of these 94 fetuses four, one pair, and two singles, both second in order of birth, were stillborn. The pair of twins were syphilitic, the singles in twins died of asphyxia during a breech extraction, and from intracranial hemorrhage during a midforceps delivery. For these two operative deliveries no indication is recorded, other than to deliver a second fetus. In each instance the first fetus had been born spontaneously. In the United States Birth Registration area for 1933, in 4.5 per cent of twins both fetuses were born dead and in 4.2 per cent, one fetus of twins was born dead.

SYPHILIS

While the Bureau study showed 95 per cent reporting as to whether a Wassermann reaction had been made, in our series only slightly over half, 106 cases, showed this serologic test to have been applied. Of these only three were positive. There had been no antenatal treatment in these cases, and the fetuses at autopsy, including one set of twins, gave unmistakable evidence of syphilis. In the remaining cases there is no record of the test or it was applied after the delivery of a dead baby.

In the South Carolina study on maternal welfare it was shown, in contrast to these figures, that 22 per cent of the clinic patients had positive serologic tests, while McCord, in a series of fetal autopsies in Atlanta, reported 57 per cent with positive findings of syphilitic infection. Such figures show the broader implications of a nationwide survey or on a smaller scale, of a city wide survey, where the regional discrepancies in types of patients may be merged into a fairly approximate picture.

Parran feels that with universal serologic tests on all pregnant women, and with appropriate antenatal treatment, new cases of congenital syphilis could be eradicated in a decade.

PREVIOUS STILLBIRTHS

It is not without interest to inquire into the previous histories of the women in this series for whom at least one previous stillbirth was recorded on the birth certificates. They number 18, or approximately 8 per cent of the series.

In 6 no cause was elicited or recorded for the previous stillbirth or stillbirths. In 4 nephritis had been present. In one there had been 8 stillbirths. In one a cesarean section had resulted in a dead baby after a long first labor. In this second pregnancy the uterine scar ruptured to produce a second stillbirth. Two were syphilitic. In one each there was previous dystocia, diabetes, repeated miscarriages, pelvic infection, pelvic injury. Undoubtedly, enough attention had not been paid to the previous history to prevent a stillbirth in the present pregnancy.

In the histories of 80 multiparous women who died after giving birth to a dead fetus, shown in random files pulled from the Philadelphia maternal mortality study, there were no significant facts in slightly over one-fourth of the cases, but the remainder had histories of previous dystocia, operative deliveries, toxemias, nephritis, repeated stillbirths or miscarriages, large babies, or even extreme multiparity, 6 to 16 pregnancies, items single or combined to form a total of 75. Certainly this was a sufficiently suggestive background to have provided enough warning that both baby and mother should not have been lost.

COMPLICATIONS OF PREGNANCY

So far as the complications of pregnancy as a productive factor in stillbirths are concerned, it is not possible to obtain them fully in this series. Many of the patients were in charge of private physicians, and their prenatal records, although added to the chart by compulsion of an order of the Pennsylvania State Board of Medical Education and Licensure, are frequently incomplete.

In the charts, 80 in number, where such notations were made, it was found that 24 women had a history of vaginal bleeding, these were almost all in the group from the twentieth to twenty-seventh week, there were 4 instances of abruptio placentae and 5 of placenta previa. In the toxemia group there were 12 cases of toxemia, of which 4 patients had convulsions, 4 had hypertension only, and 7 had nephritis. There were 6 instances of diabetes, 1 of cardiac disease, and 1 of hyperthyroidism. There were single instances of fibroids, pyelitis, tuberculosis of the spine, influenza, appendicitis, and fracture of the dorsal spine. In many, probably the majority of these complications the abnormal or associated morbid condition played a definite contributing influence toward a stillborn fetus.

In the Philadelphia report on maternal mortality of 1931 to 33 it was noted that the direct puerperal causes of death were associated with 349 contributing obstetric or medical conditions, equal to 54.6 per cent of the puerperal deaths. Just as complications of pregnancy influence the outcome for the mother so they also act for the fetus. In examining the records of the Cook County Hospital in Chicago, Allen and Bauer found the gross fetal mortality rate among normal patients to be 1.8 per cent while among patients with a concurrent medical condition it rose to 3.7 per cent. In other words a child born to a woman suffering with a medical disease is twice as likely to be stillborn as a child born to a normal woman.

Information regarding the use of drugs and anesthetics during labor and delivery is requested in the Children's Bureau schedule. In reviewing the cases in this series from this standpoint, I have analyzed critically the cases in which definite fetal or maternal states or operative manipulations did not apparently cause the fetal death. It would not be a quickly accomplished task to affirm that the Gwathmey method here, or the use of barbiturates there, or inhalation anesthesia, gas or ether, has caused any individual fetal death. Many times the same technic of sedation or anesthetization has been used safely; therefore in the deaths with obvious causative factors missing, one hesitates without more personal knowledge of

the minute details of the situation, to ascribe the fetal death to drugs or anesthetic agents. Such obscure cases must be discussed early when all the unwritten but observed data can be freshly reviewed for an impartial decision. This is a function of hospital obstetric staff conference. Such deaths as might have been due to sedative drugs or anesthetic agents therefore have been ascribed to the "no cause given" group. The uterine stimulating agents, derivatives of the pituitary gland, have been so sparingly used during labor that they can be ruled out as causes of fetal death in this series.

There were 66, or 30 per cent, macerated fetuses in this series, 24 from the twentieth to the twenty-seventh week, 19 from the twenty-eighth to the thirty-fifth week and 23 from the thirty-sixth to fortieth week or over. Of these macerated fetuses, 46, or 72 per cent were autopsied. Even with this aid to diagnosis no cause was found for the fetal death in 15 cases. The various degrees of toxemia, including nephritis, accounted for 15 cases, cord difficulties for 4, diabetes for 3, hemorrhage conditions for 5, and antenatal fetal toxemia in intercurrent influenza for one, with other varied unit items. Maceration represents varying degrees of autolysis of the fetus; its extent depends upon the length of time the child has been dead, and may vary from maceration of the cutaneous surfaces only to such complete maceration of the entire body that the fetus appears as a sac of fluid. Although it is difficult to ascertain cause of death even by autopsy in the extreme degrees, maceration should be regarded only as an effect of the death and every effort made to determine the original cause. Strachan cautions regarding the x-ray picture of the long bones in macerated fetuses stating that maceration produces an appearance in the long bones quite similar to the osteo-enchondritis of syphilis.

AUTOPSY

We were fortunate in obtaining 132 autopsies, 57 per cent, in this series of 228 stillbirths. This figure is only slightly below the autopsy percentage of the general hospital deaths. Such examinations made definite the cause of death in a majority of the operative cases, particularly was it effective in demonstrating the effect of birth trauma upon the fetal cranial contents. In only four autopsies was an examination of the brain refused. The value of examination of this organ at autopsy as contrasted with a series of autopsies in which the brain was not examined is shown in the report of Fenton. In his first series of autopsies in which the brain was included, intracranial hemorrhage was shown to be the largest cause of death. In a second series where the brain was not examined, passive hyperemia, 33 per cent, led as a causative factor of death having increased from fifth place, 11 per cent, in the first series.

In many cases where at autopsy intracranial damage is so slight as to appear unlikely in having caused the fetal death, Holland ascribes the etiology to a traumatic cerebral asphyxia. A spinal tap showing bloody fluid immediately after birth of a freshly dead fetus often gives strongly suggestive evidence of a suspected intracranial hemorrhage. A routine x-ray of all freshly dead fetuses, at least of the head in forceps cases and the spinal column, in addition, in breech cases will often throw light on the cause of the death where autopsy is refused.

CAUSES OF DEATH

The causes of death in this series have been classified according to the causes of stillbirth given on the reverse of the proposed stillbirth certificate. These are divided into, (A) causes determined in the fetus and (B) causes and conditions

in the mother associated with the fetal death. The causes determined in the fetus are divided into six groups:

A.		
1. Infections		5
Syphilis	4	
Septic infection	1	
2. Asphyxia		37
Separation of placenta	13	
Abnormalities of cord	17	
Other causes of asphyxia	7	
3. Congenital Malformations		14
Hydrocephalus	2	
Anencephalus	9	
Spina Bifida	1	
Other malformations	2	
4. Birth Injury		76
Malpresentations	7	
Difficult labor	62	
Other causes of physical injury to fetus	7	
5. Other diseases or conditions affecting the fetus primarily		39
Prematurity	38	
Quinin poisoning	1	
6. Cause unknown		28
Fetus at term		
Total		199

This list includes 199 fetal deaths in which the primary cause was recognized as such, or as in the prematures, below twenty-eight weeks, or in the full-term infants, no primary maternal cause was noted in the records.

B. Under the causes and conditions in the mother associated with the fetal death are listed 16 groups of diseases or conditions which closely follow the groupings of the International List of the causes of death.

1. Infections		5
Influenza	1	
Tuberculosis	1	
Syphilis	3	
3. Endocrine and other general diseases		7
Diabetes	6	
Thyroid	1	
7. Disease of circulatory system		3
Diseases of heart	1	
Diseases of arteries	2	
8. Disease of respiratory system		1
Bronchitis	1	
9. Diseases of digestive system		2
Appendicitis	1	
Intestinal obstruction	1	
10. Diseases of genitourinary system		10
Known to have preceded pregnancy		
Nephritis	7	
Bicornuate uterus	1	
Fibromyomata uteri	2	
11. Diseases of pregnancy and childbirth		27
Sepsis—observed before delivery	1	
Albuminuria, eclampsia and pyelitis	12	
Other toxemias	1	
Hemorrhages (Placenta previa, 9)	12	
Rupture of uterus	1	
13. Conditions of bones interfering with normal labor		1
Fracture of dorsal spine	1	

This group of conditions, 56 in number, comprises some reduplications in the groups on toxemias and hemorrhages.

The group of fetal deaths listed under difficult labor, 62 in number, includes 42 cases of lacerations of the tentorium or falx, and various types of intracranial hemorrhages, as well as 3 cases of fractured skull, all parietal bone injuries, and one fracture of the cervical spine. The diagnosis of birth trauma in the sixteen remaining cases was either grossly evident or suggested by bloody fluid on spinal puncture.

The causes in this series show, as has been so often stated, that birth injury is one of the most important factors in the production of stillborn infants. This group of deaths in large part must be ascribed to bad obstetrics. The second largest group is made up of unexplained fetal deaths before the period of viability. Whether an intensive investigation of such premature stillbirth deliveries would throw light upon the etiology of this group remains an open question. Many of the case records in this group contain a notation that bleeding was noted at the onset of labor, yet they did not present the clear-cut clinical picture of premature separation of the placenta. Closely allied is the third largest group, stillbirths at term without a cause easily obtainable, from clinical record or autopsy, if one was performed. From the maternal standpoint, chronic renal lesions and toxemia play a large part, 34 per cent, with hemorrhages, 20 per cent, closely following them.

What part does senescence of the placenta, or placentosis as some obstetric pathologists term it, apart from the gross infarction common in the nephritis group, play in the group of deaths at term without any apparent cause. Certainly if we wish to exhaust all our resources in an investigation of such deaths we must consider the pathologic physiology of the placenta in the etiology. The studies of Goodall and others suggest such a condition as a premature senility of the placenta is a very likely factor not only in some of the unexplained stillbirths at term but also in the repeated or habitual death in utero just short of term.

There are two questions which arise in the management of a known dead fetus in utero. If the patient is not in labor, when and by what means is labor to be induced. In the majority of such cases labor occurs within a short time after fetal death. Dippel records retention of a dead fetus in utero for sixty-one days before expulsion occurred. Few systemic symptoms are noted in the average case.

The second question arises with the death of the fetus during labor. Aside from conditions which necessitate immediate delivery as placenta previa or other imperative situations under what circumstances should operative delivery be performed.

There is a definite relationship between the degree of antenatal care and the stillbirth rate. Brand states that 20 per cent of fetal deaths, collected observations, occur during the antepartum period. Analyzing the figures on antenatal care from the Fifteen States Survey, he shows that women who received Grade 1 or 2 prenatal care had 70 per cent

livebirths, Grade 3 had 63 per cent livebirths, and those with no care at all 58 per cent livebirths. Hence, he concludes, on a conservative estimate three-fourths of the 20 per cent antepartum period fetal mortalities could have been prevented by more efficient antenatal examination and care.

In a maternity hygiene program in Williamson County, Tennessee, the stillbirth rate in a supervised group, representing 42.8 per cent of the total reported births in the area studied was 16.2, over a period of six years. During these years the stillbirth rate for the unsupervised group, 41.8, and the state at large 44.9, were 2.6 and 2.8 times greater than that in the supervised group. On the other hand although only one-third of the women dying in association with stillbirths in the Philadelphia Mortality Study had received adequate prenatal care, inadequate prenatal care was regarded as an almost negligible avoidable factor in the death of the mother.

Our hospital standard of febrile morbidity is that accepted by many institutions, 100.2° F., twice in any one day or on consecutive days following the first twenty-four hours after delivery. Applying this standard the general average febrile morbidity of the hospital for several years has run slightly over 11 per cent, including extragenital as well as genital causes. In this series of 228 there was an associated febrile maternal morbidity in 43 cases, 18 per cent.

There were three maternal mortalities in this series of 228 women with stillbirths. Two women died of sepsis, one following an illegally induced interruption of pregnancy at the twenty-second week; one following a version and extraction; a third woman died of hemorrhage from placenta previa.

TABLE II. TIME OF FETAL DEATH IN RELATION TO LABOR AND OPERATION

		LABOR		OPERATION		NUMBER OF CASES	PER CENT OF DELIVERIES ASSOCIATED WITH STILLBIRTHS
		BEFORE	DURING	BEFORE	DURING		
Total	228	78	136			7895	Rate: 28.8
Spontaneous	127	62	51			4925	2.5
Operation	101	16	85	37	64	2970	3.4
Low Forceps	18	6	12	7	11	1908	0.9
Mid Forceps	20	2	18	5	15	618	3.2
High Forceps	11	1	10	1	10	40	27.0
Breech Extraction	16	3	13	4	12	110	14.5
Version	20	1	19	8	12	48	41.6
Cesarean Section	11	3	8	7	4	241	4.5
Craniotomy	5	0	5	5	0	5	100.0
Not Recorded	14						

SUMMARY

A stationary stillbirth rate demands more attention. Uniform statistical practices are desirable. The proposed standard certificate for stillbirth should hasten the adoption of uniform practice by states,

cities and clinics. The Children's Bureau study should be assisted. Similar city wide studies might be desirable. Local studies in individual hospitals would encourage better obstetrical practice both in the antepartum and intrapartum periods to the benefit of the fetus.

In this series of 228 fetal mortalities birth trauma is again shown to be the largest single factor in the etiology. There is a large group of unexplained stillbirths, in both viable and previable fetuses. More intensive studies of fetus at autopsy, placenta by histology and mother or parents by clinical investigations should solve some of these deaths. From the maternal aspect, the toxemias, nephritis and hemorrhages are the principal causative factors.

REFERENCES

Tandy, E. C.: Am. J. Public Health **27:** 161, 1937. *Sterling, B.:* Public Health Reports **46:** No. 5, 1931. *Peckham and Kuder:* AM. J. OBST. & GYNEC. **27:** 537, 1934. *McCord, J. W.:* A. M. A. J. **88:** 626, 1937. *Allen and Bauer:* AM. J. OBST. & GYNEC. **31:** 885, 1936. *Goodall:* Am. Gynec. Soc. Trans. **59:** 161, 1934. *Brand, W. W.:* Ohio M. J. **21:** 24, 1935. *Dippel:* Bull. Johns Hopkins Hosp. 524, 1934.

BONE CHANGES IN THE FETUS FOLLOWING THE ADMINISTRATION OF DICALCIUM-PHOSPHATE AND VIOSTEROL TO THE PREGNANT MOTHER*

GEORGE C. FINOLA, M.D., RUTH A. TRUMP, B.S., AND MOZELLE GRIMSON, B.S., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Northwestern University and St. Luke's Hospital)

A SURVEY of the literature reveals a paucity of information upon the subject of bone changes in the fetus following the administration of calcium, phosphorus, and vitamin D to the pregnant mother.

Romaniello (1933) in a small series of 8 controlled cases, reports an increased bone density, smaller fontanels, narrower sutures and an increased birth weight in those babies whose mothers had been subjected to moderate doses of vitamins during pregnancy. Booher and Hansmann (1931) studied calcification of the tibia in 8 normal dead newborn (delivery accidents) and found that the calcium content varied slightly despite large doses of calcium, phosphorous, and vitamin D ingested. Coons and Blunt (1930) in an equally small series state that x-ray studies of the wrists and ankles of the newborn showed a tendency toward cupping in the distal ends of the ulna, flattening of the ends of the other long bones, and poor calcification of the epiphyseal ends of the diaphyses paralleling the bad calcium and phosphorous retention of the mothers.

Schmitz (1931), Fehling (1877), Michel (1899), Hugouneng (1900), and others analyzed the mineral content of the aborted fetus at various periods of gestation and while these figures varied, in general it may be said that the fetal content increased many times in the last three months of pregnancy.

*Presented before the 507th regular meeting of the Chicago Gynecological Society, March 19, 1937.

Coons and Blunt (1930) reported mineral balances on a number of pregnant women at various periods of gestation, revealing a positive calcium balance in nearly all cases, but the amount of calcium varied, the greater retention occurring toward the end of pregnancy. They found that the amount retained equalled only the estimated fetal requirements in 3 patients while in 6 it was decreased, thus indicating that these women were depositing only small amounts of calcium in the fetus or were using their own reserves to meet the fetal needs.

Baur, Aub and Albright cited by Madden (1933) advance the theory that calcium is stored in the trabeculae of bones in readily available and sufficient quantities for fetal use. Madden states that the fetus in utero rarely, if ever, suffers from the lack of calcium, and it is extremely doubtful if prenatal rickets ever occurs. Bernheim (1933) states that there is a large supply of calcium present in the maternal bones and this store can be drawn upon over a considerable period of time without producing obvious osteoporosis or a reduced content of the blood.

Mull and Bill (1932), from a review of the literature, found that there still exists a wide diversity of opinion as to what changes in the serum calcium if any, actually occur during pregnancy. Investigators accept a range of 9 to 11 mg. per hundred c.c. as the normal total serum calcium concentration and 3.7 mg. per hundred c.c. for the inorganic serum phosphorous in the blood. Morley (1913) reported a lowering of the serum calcium during late pregnancy, labor, and the puerperium. Widdows (1923) followed individual cases over an extended period of time and concluded that there was a tendency toward a decrease in the calcium content of the blood in late pregnancy which was not manifest in all cases. Cantarow, Montgomery, and Bolton (1930) summed up the literature with the conclusion that the total serum calcium diminishes during the later months of pregnancy, but is usually above the lower limits of normal. They attributed symptoms of calcium deficiency to variations in the diffusible and nondiffusible forms. Andersch and Oberst as late as 1936 studied the diffusible and nondiffusible calcium in pregnancy and concluded that the average values for these forms are fairly constant irrespective of pregnancy, and that the reported variations are due primarily to changes in the total calcium.

In regard to the calcium concentration in the fetal blood there is entire agreement. Serdyukov and Morosova, Bock and Bokelman, and Hellmuth all found the fetal concentration definitely higher than the maternal, the first named to the extent of about 20 per cent.

Sherman (1931) considers 0.45 gm. of calcium per day as the actual body requirements, but for safety, this minimum for an adult should be increased to 0.75 gm. per day. During pregnancy, however, the calcium requirements of women are greatly increased especially in the last trimester, and it is estimated that 1.6 gm. per day are the optimum requirements. The physiologic need for phosphorous has been shown to be 1.5 to 2 gm.

That the calcium and phosphorus metabolism is influenced by many factors has been pointed out by various observers; thus the source, the presence or absence of unfavorable elements simultaneously ingested which may unite to form insoluble salts, the hydrogen ion concentration in the stomach and small intestine, the activity of the parathyroid glands, vitamin D, and possibly vitamins A and C.

There are many forms of calcium on the market. Dicalcium-phosphate is said to be an excellent source, particularly because the calcium and phosphorous are present in approximately the same relationship as that found in bone.

In the present investigation 75 women at various stages of pregnancy were selected for observation. Seventeen of these were later dropped for lack of cooperation. Thirty-three were used for treatment and 25 with approximately the same weight, gravidity and expected date of confinement served as controls.

All of the patients were instructed on the so-called basic pregnancy diet which contains 1.5 to 1.85 gm. of calcium and 1.5 to 2 gm. of phosphorous per day, and each was requested to return weekly reports of

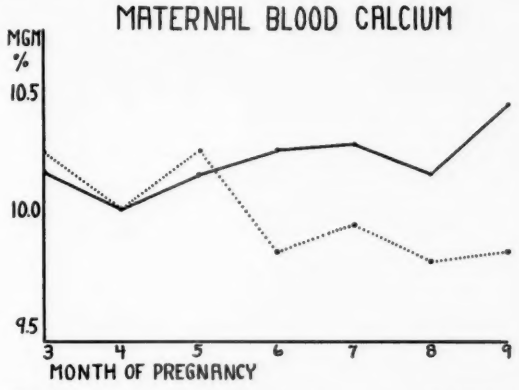

Chart 1.— ———Treated group. ..... Controls.

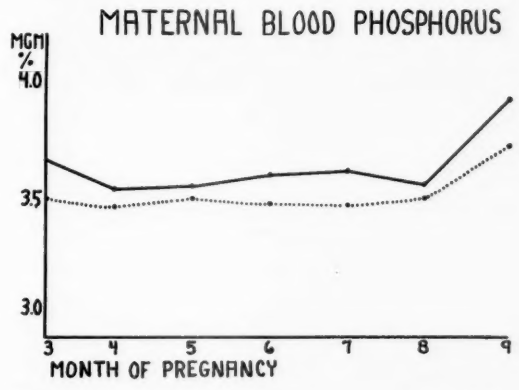

Chart 2.— ———Treated group. ..... Controls.

all foods, together with the quantity consumed between visits. To those in the treated group, the diet was supplemented by dicalcium-phosphate (dulcet bars) in doses of 6 segments (1.44 gm. calcium, 1.08 gm. phosphorous), and 30 drops of viosterol (250 D) per day. To assure ourselves that the amount prescribed conformed with the quantity actually taken, they were requested to return their boxes at fortnightly intervals so that all bars could be recorded or accounted for and a fresh supply re-issued.

Blood samples for calcium and phosphorus determinations were obtained from each patient upon her first visit, and subsequently at

TABLE I. CONTROLS. BLOOD CHEMISTRY

	1 MO.		2 MO.		3 MO.		4 MO.		5 MO.		6 MO.		7 MO.		8 MO.		OVER-DUE 9 MO.		DELIVERY		CORD BLOOD	
	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.
T. B.									9.80	4.30	10.24	3.90	9.30	3.84	10.25	3.80			10.35	4.06	11.80	7.20
B. N.							9.60	3.40														
P. B.									9.70	3.04	10.35	3.00										
C. A.											10.50	4.07	10.00	3.50	10.00	3.50			10.00	4.10	11.86	5.21
F. J.									10.20	3.70												
A. B.					10.10	3.60																
H. R.							10.00	2.90	10.30	3.76												
M. R.											9.00	3.19										
A. T.											9.80	3.80					Prem. Twins		9.75	3.86	10.55	
																					11.00	
C. N.									9.70	3.26	9.85	3.66							9.70	3.60	11.56	3.60
C. C.											10.50	3.58	10.65	3.10	9.60	3.00			9.06	3.00	11.41	4.10
C. R.							10.40	3.54	10.45	3.58												
D. S.									10.40	3.56												
E. N.									10.30	3.30												
A. S.							10.85	4.03														
M. E.															10.50	3.74			8.94	2.98	10.88	4.10
G. B.													9.10	3.81	9.55	2.98			9.60	3.20	11.42	5.00
E. G.							9.70	3.80	9.80	3.74	10.00	3.64	9.40	3.04	9.90	3.65	10.00	3.46	9.70	3.98	11.50	6.42
F. P.									10.55	2.82	9.75	3.42										
A. C.									9.85	3.30	10.31	3.54			10.00	3.04			10.65	3.86	12.20	8.10

TABLE I—CONT'D

	1 MO.		2 MO.		3 MO.		4 MO.		5 MO.		6 MO.		7 MO.		8 MO.		OVER-DUE 9 MO.		DELIVERY		CORD BLOOD	
	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.
S. S.									11.80	3.18	9.60	3.75										
A. C.									10.40	3.46	9.85	3.34										
H. B.							10.55	2.66														
F. L.							11.10	3.66														
M. M.							8.92	3.72	9.74	3.68	9.40	3.10										
J. M.									10.50	2.94												
J. W.							8.90	3.12														
B. T.									10.90	3.52	9.80	3.54	9.80	3.96					9.80	3.80	11.74	4.00
M. B.							10.05	3.04	10.53	3.72												
T. M.																						
C. S.			10.60	3.78	10.45	3.40	10.55	3.54	10.80	3.32	10.00	3.14	10.00	3.10	9.96	3.12			10.60	3.96	12.06	5.68
M. F.											9.60	2.98	10.65	3.90	9.94	3.96			9.90	4.60	11.50	5.96
G. W.											9.80	3.54	9.50	3.60	9.80	3.58			10.60	6.06	11.30	9.60
A. L.							9.40	4.20	9.55	4.12	10.20	3.98	9.74	3.90	9.74	3.90			9.70	3.70	11.84	5.76
M. D.									10.50	3.68	9.35	3.62	11.05	3.04					10.10	3.44	11.75	5.66
J. S.									10.50	3.20	9.56	3.85	10.80	3.62	11.00	3.74			9.86	3.66	12.04	6.50
M. Z.											10.40	3.06	9.60	3.20	9.05	3.10	10.20	3.40	10.10	3.56	11.80	5.42
H. R.									9.60	3.84	9.89	3.26	10.00	3.64	9.76	3.24			10.30	3.72	11.30	4.80
L. P.											9.10	2.98	9.35	3.12	9.26	3.00			9.40	3.06	11.04	5.00
R. M.											8.90	3.20	8.70	3.46	8.50	2.96	8.50	3.50	8.46	3.00	10.50	4.60
M. L.											11.00	3.54	10.10	3.16	10.00	3.50			9.90	3.20	11.06	5.00
Average			10.60	3.78	10.23	3.50	10.00	3.47	10.25	3.50	9.81	3.48	9.93	3.47	9.78	3.49			9.84	3.72	11.50	5.88

TABLE II. DI CALCIUM-PHOSPHATE VIOSTEROL GROUP, BLOOD CHEMISTRY

	1 MO.		2 MO.		3 MO.		4 MO.		5 MO.		6 MO.		7 MO.		8 MO.		9 MO.		DELIVERY		CORD BLOOD	
	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.	CAL.	PHOS.
M. De.											10.00	3.58	9.40	3.58	10.25	3.60			9.56	2.50	10.88	4.10
S. M.									10.00	4.13	9.80	3.16	10.50	3.48	10.65	3.44			10.37	3.30	11.25	9.10
V. D.							10.10	4.32	9.75	4.00	10.30	4.10	10.55	4.00	10.69	3.84			10.55	2.86	12.85	4.14
R. D.											9.75	3.10	10.30	3.00	10.90	3.86			9.36	3.22	12.05	5.20
L. M.							10.10	4.07	9.40	3.00	10.85	4.22	10.10	3.56					10.50	4.30	11.40	6.88
M. B.							9.80	3.30	10.80	4.00	10.15	4.00	9.51	3.20	9.85	3.18			10.70	4.12	11.80	5.28
H. L.									9.45	3.50	10.70	3.96	10.65	3.96	10.00	3.96			11.55	4.46	11.70	6.20
E. H.									10.90	3.80	10.60	3.73	11.45	5.32	10.80	4.64			10.20	4.00	12.35	4.00
E. R.									9.60	3.18	9.90	3.20	10.85	3.82	10.00	3.52			10.80	4.20	12.80	6.20
A. L.							10.50	3.98	9.85	3.42	9.85	3.54	10.49	3.78	10.15	3.90						
C. U.							10.30	3.58	9.25	3.40	9.75	3.38										
M. W.									10.40	3.40	9.85	3.28	10.80	3.36	10.05	3.44			11.75	4.30	13.00	5.86
M. S.					10.40	3.00	9.10	3.24	9.75	3.44	10.70	3.78	10.40	2.88	9.10	3.26			11.05	4.20	12.05	11.20
E. H.									10.70	3.30	10.85	4.32	9.60	4.20	10.75	3.36	10.50	2.96	10.80	4.50	13.00	9.86
A. H.													10.20	3.96	9.65	3.52			9.68	3.97	12.27	5.56
C. S.									10.20	3.42	9.85	2.80	10.50	4.20	10.29	3.12			9.30	3.35	10.20	7.00
D. L.											10.00	3.66	10.27	3.70	10.35	3.74			10.40	3.70	11.84	4.96
G. J.							10.00	2.76	11.45	4.06	11.00	4.96	10.45	3.40	10.60	4.28	10.60	3.42	11.00	3.52	11.80	5.60
A. M. J.											10.24	3.84	10.65	4.86	10.75	3.44				3.44		5.96
A. K.							10.40	3.04	10.35	3.72	9.74	3.62	10.65	3.00	10.58	3.86	11.00	3.90				
A. E.									10.10	3.18	10.05	3.18				Prem. Twins			10.30	4.10	10.50	3.54
																					10.80	3.68
M. C.					9.90	3.54			9.64	3.68	9.40	3.46	9.25	3.60	9.25	3.26			9.85	5.40	11.85	6.00
M. A.							9.90	3.72	11.10	3.66	10.23	3.62	10.85	3.44	9.50	3.56			10.64	3.26	12.75	5.52
A. M.							10.25	3.20	10.05	3.04	10.45	3.04	9.25	3.04	9.50	3.14			9.35	3.80	12.65	7.54
R. W.											11.70	2.80			10.50	3.04			9.85	4.68	11.95	5.60
C. H.													9.76	3.44	10.30	3.74			10.00	4.46	11.00	6.94
L. H.											9.60	3.20			10.45	3.36						
I. S.									10.25	3.66	9.75	3.30	8.80	3.14	9.25	3.72			9.50	3.55	11.00	5.80
B. L.											9.70	4.40	10.00	2.76	9.40	3.42			10.72	4.26	11.75	8.36
L. S.											10.55	2.96	11.00	3.62	11.20	2.90			9.85	2.64	11.85	5.20
F. S.													10.40	2.66	10.00	3.40	10.90	3.44	12.30	4.30	13.00	5.80
M. G.							10.30	3.68	10.20	3.49	11.05	3.54	11.00	3.66	8.95	2.66			10.58	3.65	11.90	5.60
M. P.					10.20	3.46	9.30	3.42	10.10	3.68	11.20	3.46	10.50	3.42	10.00	2.70	10.00	3.50	10.00	2.90	11.90	4.92
M. A.											11.20	4.06	11.28	4.00	10.00	3.42			10.00	4.30	11.35	7.54
Average					10.17	3.67	10.00	3.53	10.15	3.55	10.25	3.60	10.28	3.61	10.17	3.55			10.44	3.92	12.11	6.15

monthly intervals throughout the pregnancy. Another sample was procured during the late first stage of labor, and cord blood was collected from the maternal end of the severed cord at birth. The total serum calcium determinations were made according to the Clark-Collip (1925) modification of the Kramer-Tisdall method, and the serum inorganic phosphorous by the method of Kuttner and Lichtenstein, applying the correction for deviation from Beers Law as determined by Bodansky.

Fig. 1.—Illustrating average bone density of ribs and epiphyses at the knee in the control group.

Some twelve to thirty-six hours after birth, roentgenograms were taken of each infant in the anteroposterior and lateral views of the skull, and the anteroposterior view of the trunk and extremities, using the same technique in all.

In Tables I and II are listed 670 consecutive total serum calcium and inorganic phosphorous estimations. Some of these patients it will be observed were dropped after one or more determinations and a few are undelivered at the time of this report. Several significant facts however

Fig. 2.—Showing hazy and indistinct upper border of parietal bone in control group offspring.

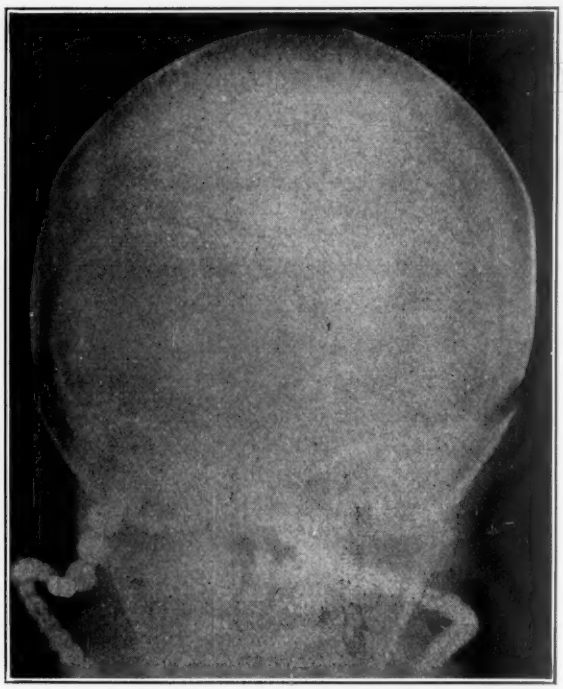

Fig. 3.—Control group showing width of fontanel.

do stand out: in the mothers of the control group there is a definite diminution of the serum calcium in the last trimester which is not apparent in the treated group; in the infants there is an increased calcium and phosphorous content of the blood over that of the mothers; and finally, these mineral levels are higher in the babies of the treated group than those of the control. Charts 1 and 2 illustrate these findings in graphic form.

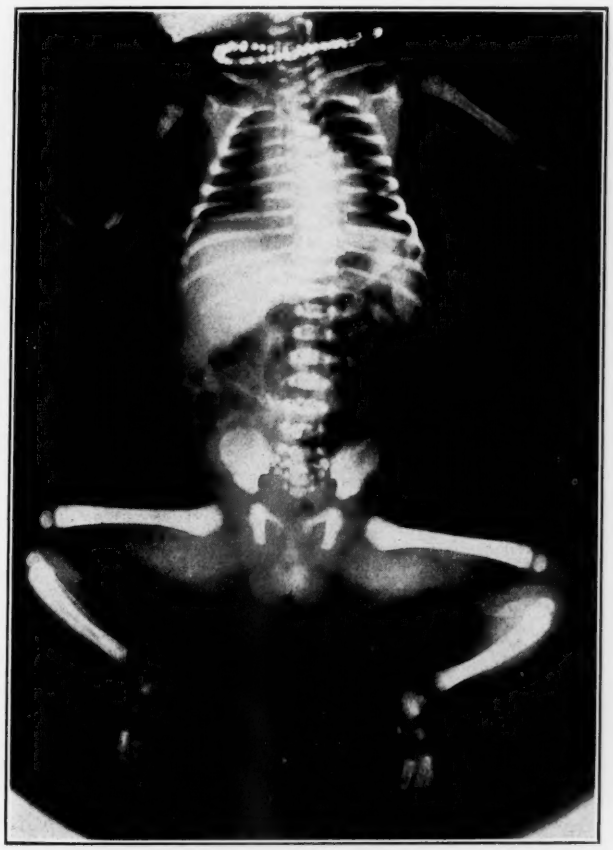

Fig. 4.—Treated group, illustrating increased density of the ribs, and increased size and density of epiphyses at the knee.

Figs. 1 to 9, selected as representative of each group, demonstrate clearly the marked tendency in the treated group's offspring toward increased bone density, especially in the ribs, the parietal bones, and the epiphyses of the long bones at the knee. The x-ray films were interpreted by Dr. E. L. Jenkinson of the Department of Radiology at St. Luke's Hospital. The ribs can be seen to stand out clearly and distinctly in the treated group, the epiphyses about the knee are larger and more dense, and of even more significance, the upper borders of the parietal bones are clear and sharply demarcated, while the ribs,

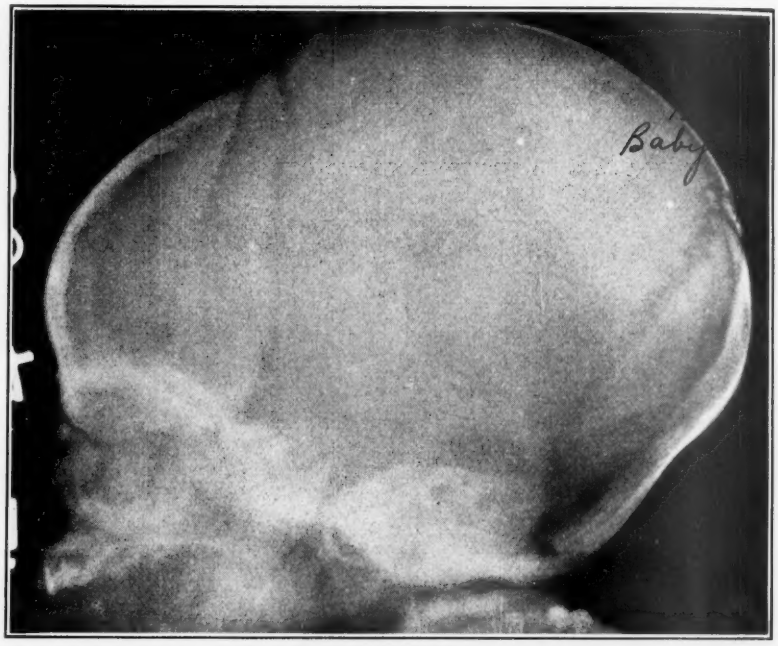

Fig. 5.—Showing sharply demarcated upper border of parietal bone in the treated group.

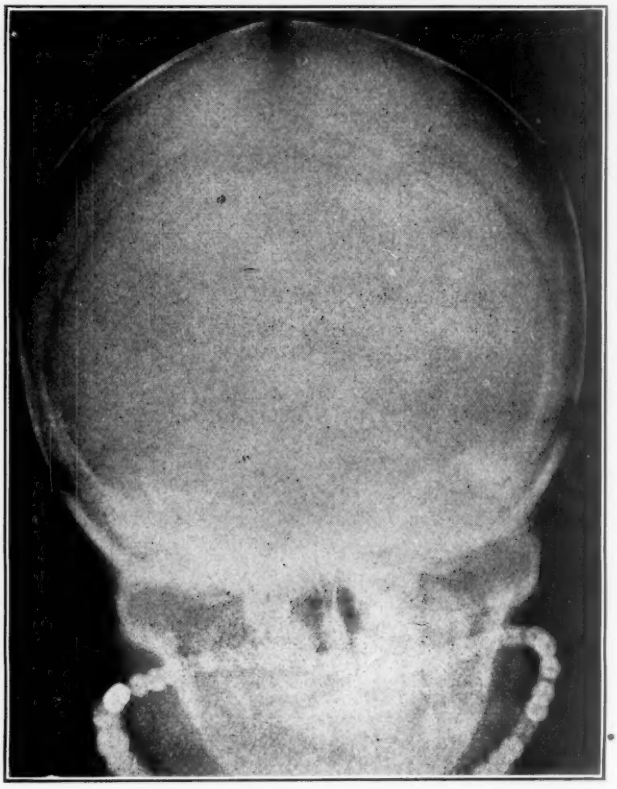

Fig. 6.—Treated group. Note size of fontanel.

epiphyses, and parietal bones in the controls are hazy and indistinct. Some unexplained variations from these results occurred as follows: 15 per cent of the mothers who seemed to have taken their medication conscientiously, showed fetal x-rays which compare only equal in bone density to that of the normal controls. Several controls showed diminished calcification below that of the average control. Only one control showed calcification equal to some of the lesser marked bone changes in the treated group.

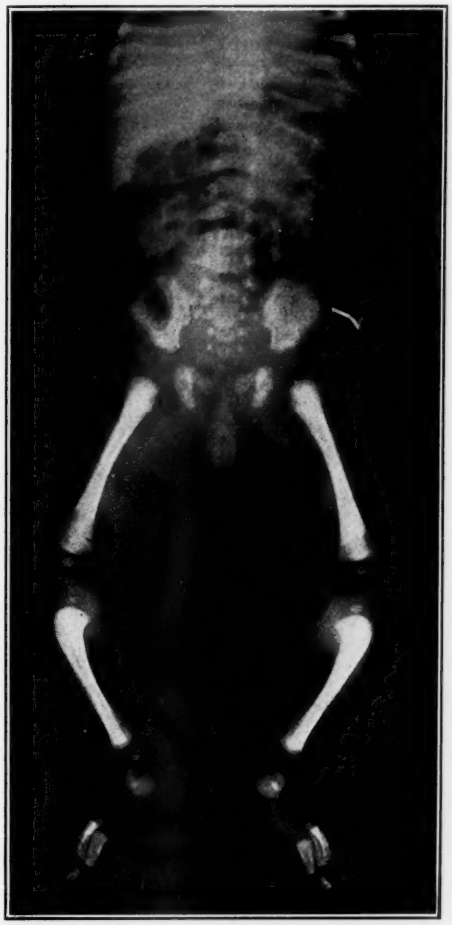

Fig. 7.—Treated group showing slight increase in size and density of epiphyses at the knee.

The average width of the fontanels, as measured from the x-ray films, was 4.6 mm. in the treated group as against 6.4 mm. in the control group. A word of caution in the interpretation of the measurements of the fontanels seems justified; many of these babies were x-rayed before the normal contour of the head, deformed by molding, had been restored, so that comparison in this series did not seem entirely reliable.

The average weight of the infant in the treated group was found to

Fig. 8.—Treated group showing dense line of demarcation at upper border of parietal bone.

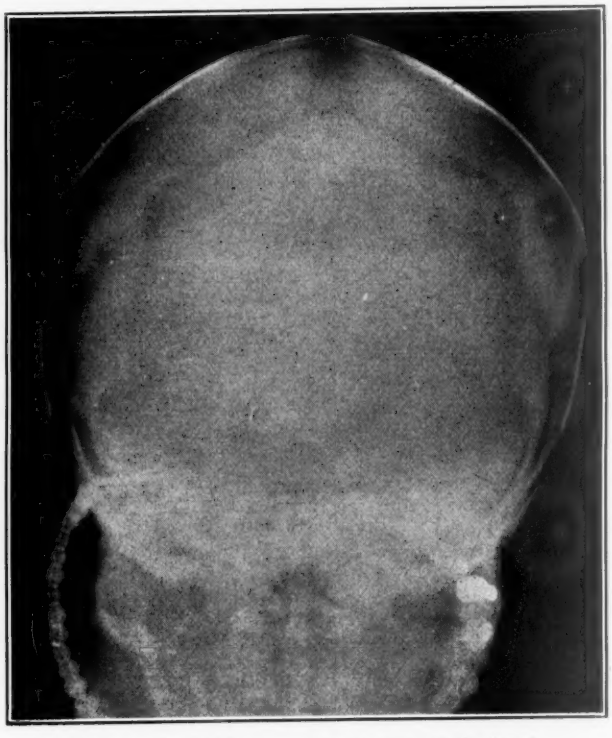

Fig. 9.—Treated group. Note size of fontanel.

be 7 pounds and 6 ounces, that of the control 7 pounds and 7 ounces.

The average duration of labor was sixteen hours and thirteen minutes for the treated group as against fifteen hours and six minutes for the controls. The number of operative interferences was found to be: 2 midforceps and 5 of the low variety in the treated group, 1 mid and 3 low in the control series.

There were no true dystocias encountered in either group but the number of cases in this investigation, we feel, is too small to warrant a definite statement as to the advisability of administering additional calcium, phosphorous, and vitamin D to the pregnant mother. However, it is reasonable to assume that with the increased density of the fetal bones, especially in the parietal region, molding which becomes an important factor in many borderline pelves may be adversely affected, and it seems justifiable to warn against the indiscriminate use of large doses of both minerals and vitamin D during pregnancy.

SUMMARY

1. Fifty-eight women at various periods of gestation were studied during the remainder of their pregnancy. Thirty-three of these were treated with dicalcium-phosphate and viosterol while 25 served as controls.

2. The total serum calcium in the treated group increased slightly during the later part of pregnancy, while in the control group there was a definite diminution.

3. The total serum calcium and inorganic phosphorous of the newborn exceeds that of the mothers. This increase is more pronounced in the treated group.

4. There is definite evidence of increased bone density in the majority of infants born to the mothers of the treated group. The sites of predilection for this increased density were found to be: in the ribs, in the parietal bones and in the epiphyses at the knee.

5. It is suggested that this osteosclerosis, especially in the parietal region, might possibly interfere with molding of the head which is so often a very important factor in many borderline cases.

These preparations were generously donated by the Abbott Laboratories, Chicago, Ill.

REFERENCES

Andersch, M., and Oberst, F. W.: J. Clin. Investigation **15:** 131, 1936. *Bernheim, A. R.:* J. A. M. A. **100:** 1000, 1933. *Bodansky, A.:* J. Biol. Chem. **99:** 197, 1932. *Booher, L. E., and Hansmann, G. H.:* J. Biol. Chem. **94:** 195, 1931. *Cantarow, A., Montgomery, T. L., and Bolton, W. W.:* Surg. Gynec. Obst. **51:** 469, 1930. *Clark, E. P., and Collip, J. B.:* J. Biol. Chem. **63:** 461, 1925. *Coons, C. M., and Blunt, K.:* J. Biol. Chem. **86:** 1, 1930. *Fehling, H.:* Arch. f. Gynäk. **11:** 523, 1877. *Hawk and Bergeim:* Practical Physiological Chemistry, 1931. *Hugouneng, H.:* J. de Physiol. Gen. **2:** 509, 1900. *Kuttner, T., and Lichtenstein, L. :* J. Biol. Chem. **86:** 671, 1930. *Madden, J. J.:* M. Times & Long Island M. J. **61:** 170, 1933. *Michel, C.:* Compt. rend. Soc. de biol. **51:** 422, 1899. *Mull, J. W., and Bill, A. H.:* Am. J. Obst. & Gynec. **23:** 807, 1932. *Romaniello, G.:* Arch. di ostet. e ginec. **20:** 535, 1933. *Schmitz, E.:* Arch. f. Gynäk. **121:** 1, 1931. *Sherman, H. C.:* Chemistry of Food and Nutrition, New York, 1931, The Macmillan Company. *Widdows, L.:* Biochem. J. **18:** 555, 1923.

DISCUSSION

DR. JAMES E. FITZGERALD.—It is very interesting that a definite change in the bony structure of the fetus can be brought about by dicalcium-phosphate and viosterol. Yet like other things that are presented to us, we do not know what to do with this information. Neither the pediatricians nor ourselves know enough about newborn babies to know whether we are doing harm or not by such treatment. The answer will depend entirely upon some one's determining what is a perfectly normal baby and whether babies with denser skulls are better babies than the ones whose skulls are not so dense.

I would like to ask Dr. Finola whether it is possible that the increase in blood volume in the later months of pregnancy would account for the decreased percentage of blood calcium. The blood may show a smaller number of milligrams of calcium per 100 c.c. because of the admitted increase in blood volume in these later months.

Too many of us prescribe medication of which we know very little. All of us have been giving calcium and viosterol probably more because of advertized suggestions than from a real knowledge of the results of this medication.

DR. FINOLA (closing).—I am unable to answer Dr. Fitzgerald's question regarding the cause of the diminution in blood calcium that occurs in the latter part of pregnancy in relation to the increase in blood volume.

A MODIFICATION OF THE LE FORT OPERATION FOR INCREASING ITS SCOPE*

J. R. GOODALL, M.D., AND R. M. H. POWER, M.D., MONTREAL, QUEBEC

THE LE FORT operation consists of a marsupialization of the vagina. Its chief application is found in cases of complete procidentia, where all supporting structures have been disrupted by the forceful descent of the hernia. This condition parallels the massive inguinal and abdominal hernias that one encounters in general surgery. In these cases, ectopic tissue has to be introduced from other parts of the body to make up the loss occasioned by the divulsion of the hernia. In massive procidentia of the genitals, marsupialization offers an easy, safe, and sure method of restoration. It has its very well-marked circumstantial restrictions, however. These are that the woman must be past the childbearing period; that she be a widow without prospects of remarriage. Its great advantages are that it is a relatively safe operation; that it can be done without spinal or general anesthesia; that the surgical risk is relatively slight; and that the results are uniformly excellent, even in the most senile cases, both generally and pelvically speaking. The greatest disadvantage of this operation lies in its restricted scope. Its greatest restricting circumstance lies in that a woman must be a widow in deed.

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

The present modification removes this second disadvantage. It is but necessary that a woman be past the menopause, or be rendered sterile at the time of operation.

The modification here outlined may or may not be preceded by a vaginal hysterectomy. This antecedent procedure will materially depend upon the healthy state, or lack of it, of the upper genital organs. The Le Fort, when preceded by a vaginal hysterectomy, must undergo a slight modification of minor importance.

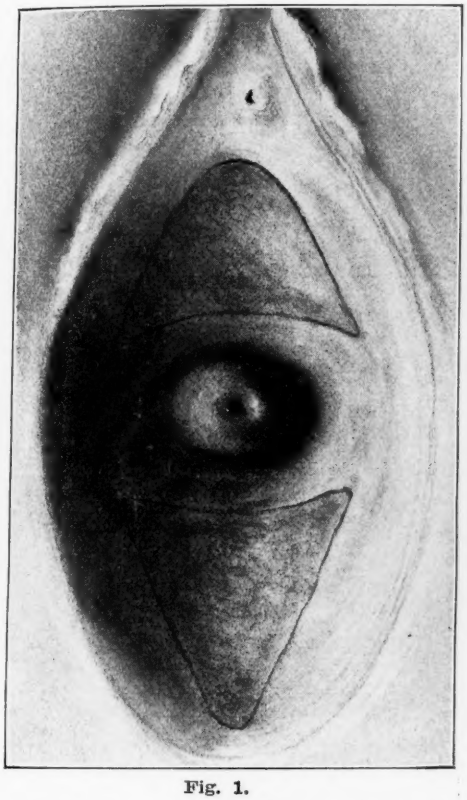

Fig. 1.

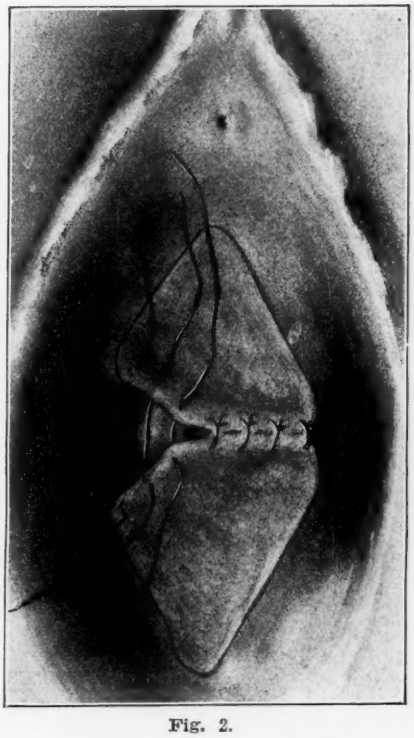

Fig. 2.

Fig. 1.—First procedure in modification of the Le Fort operation. Denudation of anterior and posterior wall in uncomplicated cases.

Fig. 2.—Suture of the bases of the denuded triangles. The right half of the cervix and external os still visible in the unclosed half.

The Le Fort as described by its author, and as presently put into practice, consists in a denudation of a long narrow triangle on the posterior wall of the vagina, and a similar one on the anterior. These denuded areas have their base near the cervix, and their acute angle near the vulva (Fig. 1). The bases of the denuded triangles in the anterior and posterior fornices should be far enough from the cervix, anteriorly and posteriorly, to permit free drainage of the cervical and uterine secretions down either of the two vaginas. The operation is completed by the complete approximation by sutures, of the anterior and posterior vaginal denudations. The suturing, as practiced by Le Fort and by the late Professor William Gardner, consisted in sewing

the bases of the two triangles together by a continuous chromic catgut suture. This first step closes off the cervix (Fig. 2) from view, and establishes the crossbar of the vagina, by which the cervix communicates with both vaginas now in the process of formation. To approximate the rest of the denuded triangles, a single suture is passed from the posterior vaginal wall a quarter of an inch outside the margin of denudation, and about one-third inch down the vagina from the basal suture, and either undermines or plicates the raw surface of the posterior triangle to its midline. The suture now picks up a corresponding point in the midline of the anterior denudation, undermines it or plicates it, eventually to emerge on the anterior vaginal wall, one-fourth of an inch from the raw surface (Fig. 3). It will depend

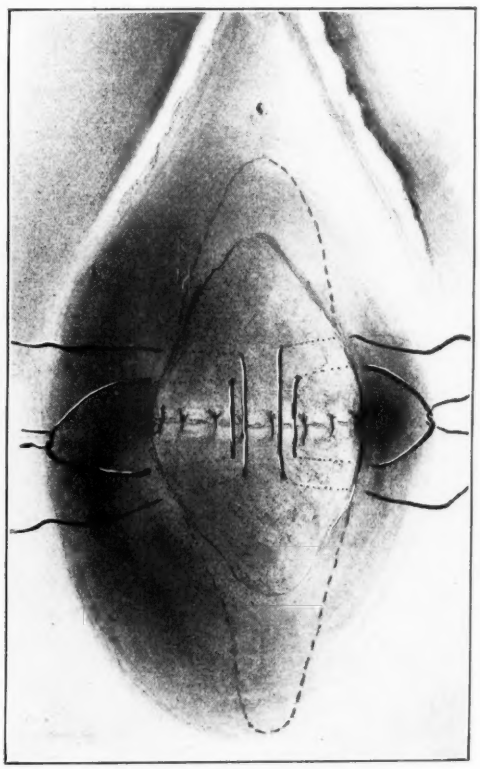

Fig. 3.—Position of the sutures for the co-aptation of the anterior and posterior denuded raw surfaces.

upon the thickness of the tissues, denoting the proximity of bladder on the anterior wall, and peritoneum on the posterior, whether one undermines or plicates. A similar suture is introduced on the opposite side. These two are now tied, just tightly enough to approximate, but not to strangle the tissues. Similarly placed sutures are continued down each side, each about one-third inch apart, until the apices of the denuded triangles are closed, the one over the other. The final result is a double vagina, beginning with the vulva and communicating above by a cross-bar below the cervix. The knots are all exposed in the double vaginal canals, and a minimum of catgut is buried to be digested—a matter of considerable importance in senile cases. The vast majority of these cases are of this age. There is no age limit to this operation. It can be done under scopolamine and morphine, and if the marsupialization is followed by a perineorrhaphy, local anesthesia of the vulva is simple and effective.

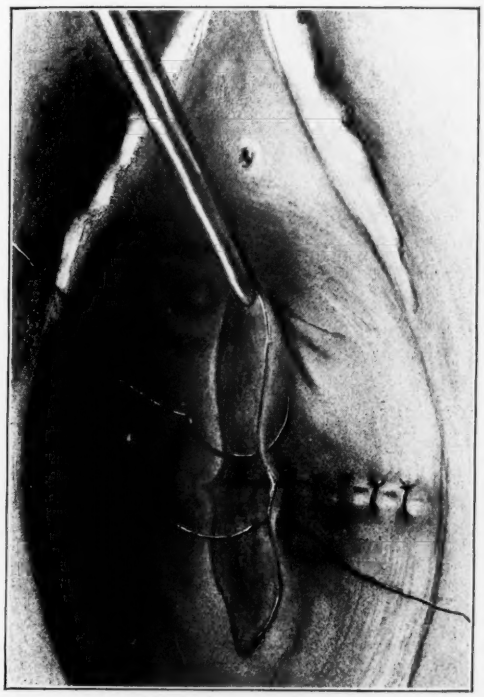

Fig. 4.—The vaults of the vagina have been closed and co-aptation of the denuded surfaces is being completed.

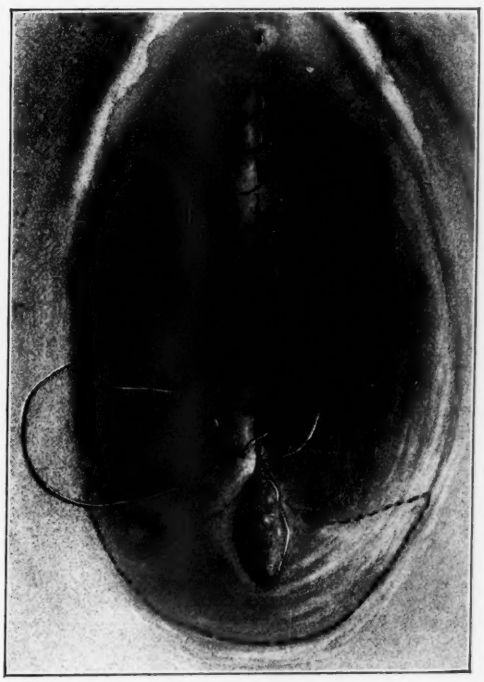

Fig. 5.—The anterior colporrhaphy has been completed below the marsupialization and the mucosa of the posterior wall is being approximated after co-aptation of the fascial layers. The further denudation for the perineorrhaphy is outlined in red.

The modification about to be described, consists of a similar marsupialization of the vagina,[1] but the base is made narrow or wide, depending upon the vaginal capacity, and[2] the apex of the marsupialization should extend down the anterior or posterior walls various distances, depending on the length of the vaginal cavity. As a rule, the marsupialization involves only the upper third of the vaginal long axis. Before the two apices are sutured together, the anterior vaginal wall below the anterior apex is opened up as in an ordinary cystocele operation, with dimensions of denudation proportionate to the size of the cystocele (Fig. 4). This is then closed by its fascial layers, and when these deep layers are closed, the marsupializing

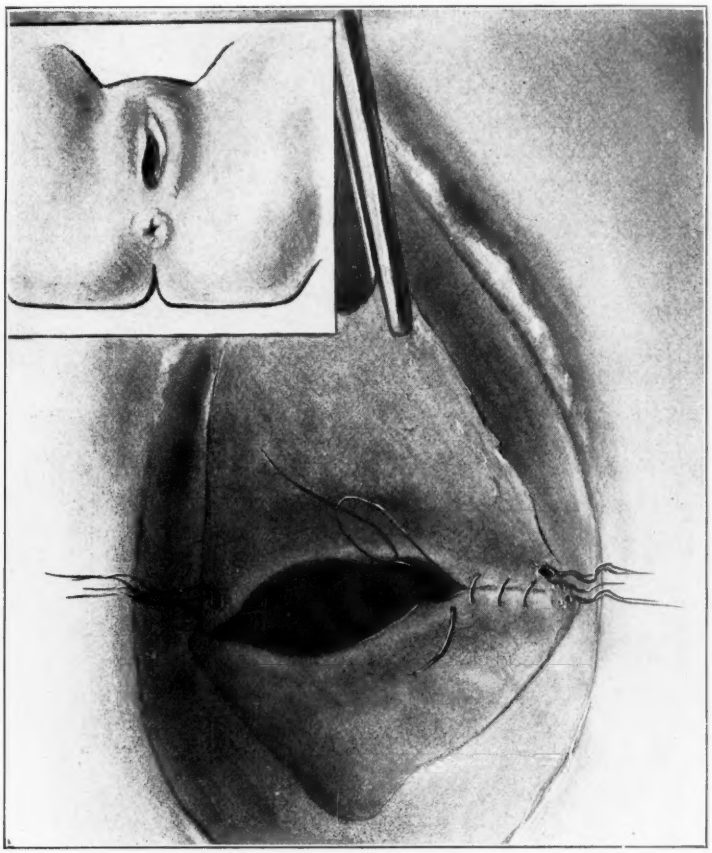

Fig. 6.—Approximation by suturing of the vesical peritoneum to the posterior parietal peritoneum, after vaginal hysterectomy. Small diagram shows the position of the patient.

sutures are continued to the posterior apex, and the mucosa of the anterior colporrhaphy is then closed. The last step of the operation consists of an extensive perineorrhaphy, the upper apex of which usually extends into the sides of (Fig. 5) the apex of the posterior marsupialization. The resultant is a single vagina for about two-thirds of the vaginal long axis, and a double vagina of the upper one-third of its length. The upper marsupialization gives the patient an irreducible fixation point to which the anterior colporrhaphy and perineorrhaphy are dependent. The end-result is surprisingly effective. I have performed the operation 24 times with uniformly satisfying results. Chromic twenty-day No. 0 catgut was used

throughout. The healing was eminently satisfactory, and there was uniform subjective satisfaction, except one case of dyspareunia due to too effective closure of the vagina. This was one of the first of the series. The ages varied from fifty-six to seventy-four years.

The modification, above described, may be immediately preceded by a vaginal hysterectomy. Under these circumstances, the technique is slightly different in its initial stages. After removal of the uterus, the anterior (vesical) peritoneum is sutured to the posterior peritoneum of the Douglas pouch by a continuous No. 1 plain catgut (Fig. 6). The suture should transfix the upper apices of the broad ligaments. The two broad ligaments are now brought together by a continuous suture

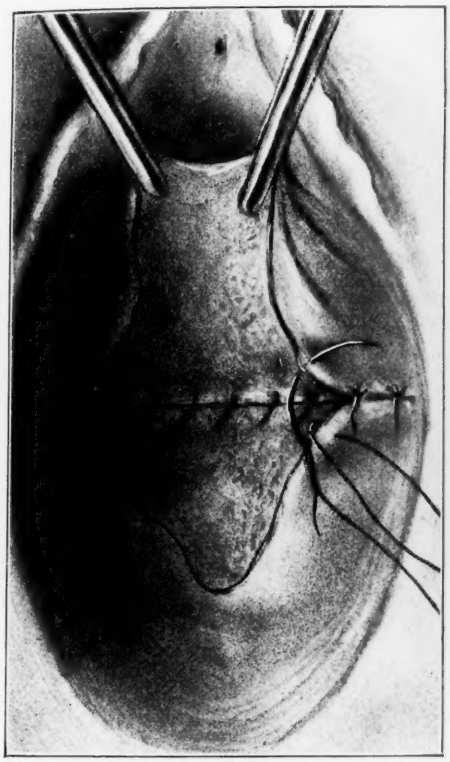

Fig. 7.

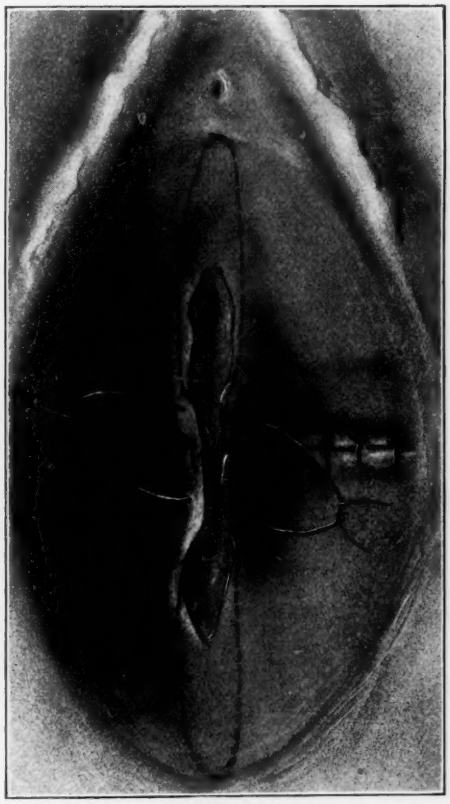

Fig. 8.

Fig. 7.—After closure of all anterior and posterior raw surfaces to eliminate dead spaces following hysterectomy, the vaginal vault is being closed with interrupted sutures and denudation of anterior and posterior vaginal walls is shown, constituting the first step of the modified Le Fort.

Fig. 8.—Co-aptation of raw surfaces and dotted outline of further denudation to constitute anterior colporrhaphy and posteriorly denudation becomes continuous with an extensive perineorrhaphy.

right down to, but not involving, the anterior and posterior vaginal incisions, so that no dead space is left in the pelvic raw surfaces (Fig. 7). One now proceeds with the marsupialization. From the anterior margin of the incision, the anterior vaginal mucosa is denuded down to the external meatus as in an ordinary anterior colporrhaphy. The upper part of the denudation seldom exceeds one inch in width, but it broadens out at the widest part of the cystocele to proportions adequate to the size of the cystocele (Fig. 8). One now picks up the posterior incision in the vault,

and denudes a strip along the whole length of the posterior wall, from about the junction of its lower and middle third up to the raw surface of the primary circumcervical incision. The denuded areas, anteriorly and posteriorly, are now continuous with each other and with the open bases of the broad ligaments (Fig. 7). One now begins to suture. With forceps placed at each lateral end of the primary incision in the right and left fornices, one sutures the anterior margin to the posterior with a series of interrupted No. 0 twenty-day chromic catgut sutures, until the bases

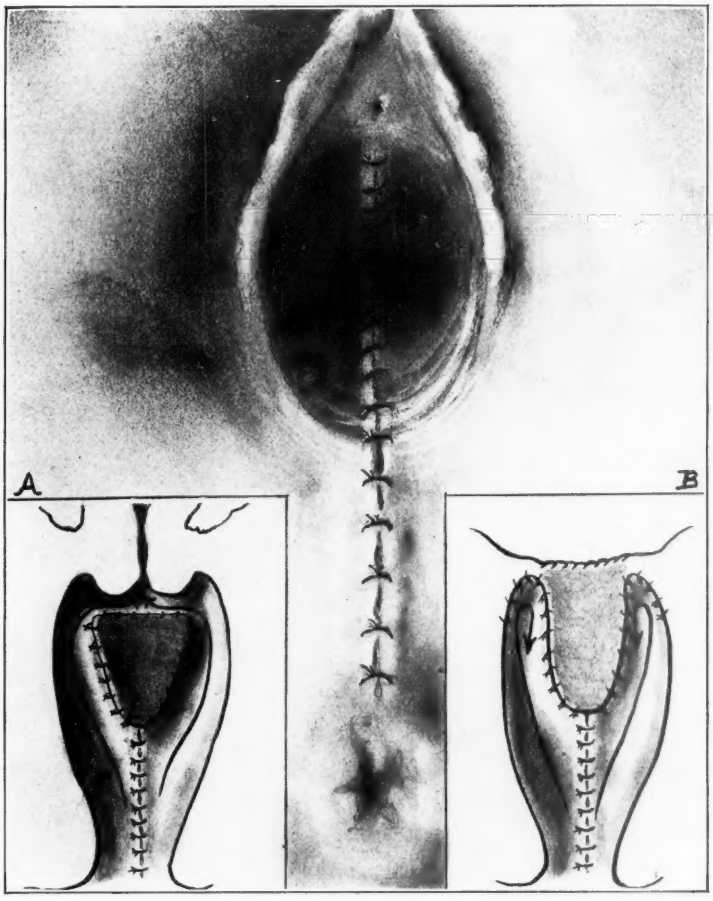

Fig. 9.—Completed appearance of the modified Le Fort, showing sutures of the anterior colporrhaphy and the extensive perineorrhaphy. The apex of the marsupialization is visible in the midline, high up in the vagina with the recesses of the double vagina visible on either side. *Inset A,* Appearance of lateral section with the completed operation where hysterectomy was not done. *Inset B,* The appearance of a similar section after vaginal hysterectomy.

of the marsupial denudation is reached on either side (Fig. 7). The further suturing is continued as described above, in the uncomplicated cases (that is, without preliminary vaginal hysterectomy).

The end-result in the complicated cases is a single vagina for the lower two-thirds of the long axis of the vagina, and a double vagina for the upper third. But they differ from the uncomplicated cases in that there is no subcervical crossbar to unite the vaginas. They end in blind culdesacs (Fig. 9).

Plain or iodoform gauze, soaked in acriflavine in oil, is now packed loosely in both vaginas and is allowed to protrude an inch or two beyond the hymen. A Malecot stay-catheter is placed in the bladder and an artery clamp is put upon it, and the clamp is pinned to an abdominal binder. The clamp is released every three or four hours, the urine drawn off, and the bladder is irrigated once in every twenty-four hours with boracic acid solution, followed by silver nitrate ⅛ to ¼ gr. to the ounce of distilled water. The vaginal gauze is removed about the fourth day, and the bowels are opened between the fifth and seventh days. Douches are not used, and enemas are taboo. Postoperative shock has not been seen, and the postoperative pain is proportionate to the tension one puts upon the sutures closing the perineal skin. Approximation is all that is necessary in skin suturing, suture tension is very discomforting, to the patient.

DISCUSSION

DR. LOUIS E. PHANEUF, BOSTON, MASS.—The modification presented adds another operation to the list of vaginal methods which may be employed in the treatment of uterovaginal prolapse. Personally, I have reserved colpectomy for those women who were advanced in years and who felt that sexual relations were not of great importance. In the future I shall be tempted to try the operation devised by Drs. Goodall and Power in the younger group of patients. I feel, that their modification will find a place in the management of large procidentias. The technic, as described, is rather simple, and should offer no particular difficulty to the pelvic surgeon.

The anesthesia which they advocate, namely scopolamine and morphine, and local anesthesia for the perineorrhaphy, is the simplest one could use and is not shocking to old women, who form the largest group for which the operation is recommended. The combination of vaginal hysterectomy and marsupialization allows one to resort to the intervention if, for one reason or another, it is deemed advisable to sacrifice the senile uterus. Loose approximation of the perineal skin, as brought out, is an essential to the patient's comfort.

In my own series, there were 21 subtotal colpectomies or Le Fort operations and 6 total colpectomies, making a total of 27. Amputation of the cervix was done 12 times and perineorrhaphy 26 times. In this group 6 patients were operated upon under local anesthesia, 9 under spinal anesthesia and 12 under general anesthesia. There was no mortality in the series. The result was satisfactory in the 6 total colpectomies and in 19 of the Le Fort operations. There were 2 recurrences in the latter group, giving a percentage of recurrence of 9.5 per cent. The ages of the patients varied from forty-five to seventy-two years.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—The original Le Fort operation leaves the uterus in, and out of the vagina are produced two small passages. The cervix is shut off from observation and the uterus is made difficult of palpation. In the event of a vaginitis it makes a cure almost impossible. Also, in the typical Le Fort operation the pull of the perineal attachment of the vagina to the anterior vaginal wall often produces incontinence of urine.

In brief, I think that an operation that eliminates two-thirds of the Le Fort principle is commendable. With this modification, there is only one-third of the Le Fort operation left and that is the upper third of the vagina with its two passages. I would say that the operation as described is about 66⅔ per cent good, and when Dr. Goodall has eliminated the remaining Le Fort principles the operation will approach 100 per cent in efficiency.

DR. FREDERICK C. HOLDEN, NEW YORK, N. Y.—I am most enthusiastic about the results I have had with the Le Fort operation, and the modification that Dr. Goodall has presented for our consideration is very interesting. Occasionally

I see a case where I could utilize this modification. In some of the cases Dr. Goodall has reported, I would, however, have chosen to do an interposition operation with sterilization.

I know of no other surgical procedure which cures so much pathology with so little surgical risk. One of my former residents did a Le Fort operation on a patient about sixty-three years of age who had complete prolapsus. The result was so excellent that the patient's widowed mother, a woman of ninety-three years, who also had a complete prolapse, insisted that the operation be performed on her. This old lady was operated upon under morphine and scopolamine anesthesia with an excellent result and lived in greater comfort to be almost one hundred years old.

DR. JOSEPH L. BAER, CHICAGO, ILL.—We are well aware of the fact that the supporting structures in the region of the upper third of the vagina anteriorly and posteriorly are comparatively feeble. Apparently therefore the cure that Dr. Goodall obtains by approximating only the upper third of the vagina, anteriorly and posteriorly, is dependent rather largely on his reconstruction of the vaginal tube in its distal two-thirds. The reconstructed pelvic floor apparently is the chief support of the prolapsed uterus which has been pushed up and held above the approximated anteroposterior upper third of the vagina. This to a certain extent substantiates the view of those who believe that prolapse can be cured solely by simple vaginal reconstruction. This is a view to which I do not subscribe.

DR. JAMES R. GOODALL, MONTREAL, QUE. (closing).—These 24 cases to which I had alluded were cases where marital relations might take place afterward. Their ages varied from fifty-six to seventy-six years. It was with the idea of overcoming the restriction of the Le Fort operation to patients not requiring the retention of the capacity for future intercourse that this modification was primarily instituted.

Many of these patients had conditions which made them rather serious risks—glycosuria, high blood pressure, and other difficulties. Some of these can be overcome prior to operation. One thing which I think deserves a great deal of attention is that all of these patients were examined as regards their basal rate, and it was extraordinary how many of them had a very low basal rate. It is well to bring that up beforehand to facilitate healing. Many patients with high blood pressure will have a fall of blood pressure when put upon thyroid almost to the point of saturation.

Regarding Dr. Baer's reference to weakness of the posterior and anterior vaginal supports, one point is to be noted. As one approaches the vault of the vagina, if one pulls on the lower apices of the marsupialization, he will find that the structures will not descend. It is upon this point that the operation depends.

Barsony, Jeno: Blood Cholesterin and Ovarian Function, Monitore ostetrico-ginecologico **8**: 397, 1936.

Barsony found that during pregnancy the cholesterin of the blood is augmented and increases as pregnancy advances. The oral administration of cholesterin increases the cholesterin blood index of normal pregnancy but does not affect the cholesterin blood index of severe cases of hyperemesis gravidarum. When cholesterin was administered to mild cases of hyperemesis, cure has always followed. The blood cholesterin is always increased in cases of fibroids and ovarian cysts. It, however, is diminished following operation, general anesthesia, and traumatic surgery.

AUGUST F. DARO.

PREGNANCY COMPLICATED BY OVARIAN AND PAROVARIAN TUMORS*

KARL M. WILSON, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology of the University of Rochester School of Medicine and Dentistry)

PREGNANCY when complicated by the presence of ovarian or parovarian tumors may at times follow an entirely uneventful course, but on the other hand extremely serious situations may arise which endanger the pregnancy and threaten the life of the patient. In the past, this has been regarded as one of the most serious complications which could occur and in the large series of 720 cases collected by McKerron in 1906, the maternal mortality was 21 per cent while the fetal mortality exceeded 50 per cent. In this series, however, only a few were subjected to laparotomy, most of the women either having had no operation or operation was limited to vaginal puncture of the cyst. Following the application of modern surgical methods to the treatment of this complication the results show a striking improvement and most authorities feel that at present the maternal mortality resulting from this complication should be less than 2 per cent. At the same time it must be recognized that the inherently dangerous potentialities are still present if the condition be overlooked or neglected.

Among the serious possibilities that may develop, the following should be particularly mentioned. Abortion or premature labor may at times occur; the pedicle of the tumor may undergo torsion, giving rise to an acute surgical emergency which may develop during pregnancy or labor, or may occur in the puerperium. Again the tumor may cause serious dystocia, at times being responsible for the occurrence of an abnormal presentation, or offering an insuperable obstacle to the passage of the child through the pelvis. This may necessitate the performance of cesarean section in order to effect delivery, or if the obstacle be not recognized, rupture of the uterus may occur. At times a cystic tumor may rupture during delivery. In the small simple cyst this may be a matter of indifference, but in certain types such as dermoids it may be attended by serious consequences. Occasionally gangrene of the tumor has occurred as the result of prolonged pressure upon it during labor.

The series herewith presented is a small one but it illustrates rather well a number of the possibilities that may occur in connection with this complication. In view of the serious results which may develop,

*Read at the Sixty-Second Annual Meeting of the American Gynecological Society, held at Swampscott, Mass., May 31 to June 2, 1937.

it has been our general policy, up to the present, to advise the removal of the tumor when possible as soon as the diagnosis was established, this being also the policy generally advocated in most clinics at the present time. The maternal results have been excellent and no maternal deaths have occurred. This series of cases may be conveniently divided into a number of groups according to the conditions present.

In the first group to mention, there were 7 cases. Operation for the removal of an ovarian tumor was carried out at various periods of pregnancy from two and one-half to five months. In each instance the convalescence was uneventful, and in each instance the pregnancy continued to term. An important point to note in this group is that in no instance was a corpus luteum found in the removed tumor, while in 6 instances it was very definitely observed in the other ovary which was not removed. In one instance there was torsion of the pedicle of the tumor. The type of tumor represented in this group included 2 dermoids, 2 simple unilocular cysts, 2 simple multilocular, and an endometrial cyst. It is interesting to note that the latter presented a striking decidual reaction, as would be expected.

In a second group are included 5 women with parovarian cysts. In four of them operation was carried out during pregnancy at seven and one-half, three months, and in 2 instances at about seven weeks, respectively. Three of them were acute emergencies with torsion of the pedicle of the cyst. In three of these 4 cases convalescence was uneventful and the pregnancy continued to term. In 1 instance however where torsion of the pedicle had occurred, spontaneous abortion occurred the day after operation. This patient, however, had had symptoms of threatened abortion for three weeks prior to operation, and when she aborted, the intact ovum was found to be defective with no visible embryo. In the fifth case the cystic tumor was discovered in the pelvis at the end of the first stage of labor. This presented a possibility of serious trouble, but the tumor was not impacted and the resident in charge, by a stroke of good fortune, was able to dislodge it manually, and spontaneous labor occurred. The tumor was removed by operation in the puerperium, the convalescence being uneventful.

In only 2 instances in our series cesarean section was necessary on account of the mechanical obstruction resulting from the presence of the tumor in the pelvis. One tumor was a dermoid, the other a simple cystoma 10 cm. in diameter. In both instances the tumor was not discovered until late in pregnancy. Elective cesarean section was carried out in each case and the tumor removed at the same time. Convalescence was uneventful in both instances. It is quite possible of course that cesarean section might have proved necessary in some of the women in the first 2 groups had the tumors not been removed earlier in their pregnancies.

On the other hand there were 3 women in our series in whom the pregnancies and labors followed an entirely uneventful course in spite of the presence in each instance of a sizable ovarian tumor. In one the tumor was not discovered until after delivery. This was removed at an elective operation in the late puerperium, and proved to be a dermoid. The convalescence was uneventful. In the other two, the tumors were discovered during pregnancy. Operation was refused, and both patients went to term and were delivered spontaneously. No complications arose during the puerperium.

In another group comprising five patients the interesting association of tubal pregnancy and an ovarian cystoma was noted. It was apparent, however, that the presence of the tumors was not a factor in the causation of the tubal pregnancy. This was evidenced by the fact that 2 of them were lutein cystomas, and probably developed after the tubal pregnancy was established. In a third the tumor, a simple unilocular cystoma, was situated on the side opposite to the tubal pregnancy, while

in the other two, which were simple multilocular cystomas and situated on the same side as the tubal pregnancy, the causative factor of the tubal pregnancy was to be found in a considerable degree of so-called follicular salpingitis. While the tumors apparently played no part in causing the tubal pregnancy, these patients are of interest on account of certain diagnostic difficulties which resulted in some of them. Typical of the mistakes likely to be made would be the diagnosis of the tubal pregnancy and the overlooking of the cyst, or vice versa. In one of our cases the cyst was diagnosed as being associated with a normal uterine pregnancy, tubal pregnancy not being discovered until the time of operation.

Much the most interesting group of patients in this series, from the physiological standpoint, are 5 women who were operated upon during pregnancy, in whom removal of the tumor involved the removal of the corpus luteum. On account of their importance they will be presented in a little more detail.

CASE 1.—(No. 6189.) A thirty-year-old para ii, six or seven weeks pregnant, presenting acute abdominal symptoms in the right lower quadrant together with a cystic mass. Operation revealed a simple cystoma with torsion of its pedicle. The tumor, after its removal, was found to contain the corpus luteum. Spontaneous abortion occurred four days after operation, her further convalescence was uneventful.

CASE 2.—(No. 48333.) A twenty-year-old para i admitted with acute right lower quadrant signs when about six weeks pregnant. An acute appendix was suspected. Operation revealed a simple cystoma, the pedicle not twisted. This tumor after removal was found to contain a recent corpus luteum. Spontaneous abortion ten days after operation, dead ovum. Further convalescence uneventful.

CASE 3.—(No. 34962.) A twenty-five-year-old para i. A left sided cyst, 8 cm. in diameter developed after her first month of pregnancy. At the third month acute torsion of the pedicle occurred. Immediate operation with removal of the tumor which proved to be a corpus luteum cyst. Spontaneous abortion eight days later, dead ovum. Further convalescence uneventful.

CASE 4.—(No. 60685.) A twenty-four-year-old para ii admitted with right lower quadrant pain, six weeks pregnant, diagnosed subacute appendix. At operation removal of an ovarian cystoma which proved to be a corpus luteum cyst. Vaginal bleeding began eleven days after operation, abortion occurring two weeks later. Convalescence thereafter uneventful.

CASE 5.—(No. 45141.) A thirty-two-year-old para 0 admitted on account of some vaginal bleeding and a sensitive mass in the L.L.Q. Ectopic pregnancy suspected. At operation, approximately five weeks pregnant, resection of an ovarian cystoma which proved to be a dermoid but also contained a recent corpus luteum. (There was congenital absence of the opposite ovary.) Spontaneous abortion five days later, dead ovum. Abortion was threatened before operation in this patient and possibly would have occurred in any event.

In our last group in the series are 3 patients, two of whom had spontaneous abortions associated with ovarian cystomas. The first one was admitted on account of severe bleeding from an imminent abortion at about the third month of her pregnancy. The abortion had to be completed artificially. A month later a simple unilocular cystoma was removed, and this was followed by an uneventful convalescence. In the second one, who was about six weeks pregnant, the diagnosis lay between a uterine pregnancy with an associated ovarian cystoma or ectopic pregnancy. There

had been some slight vaginal bleeding. At operation, a simple cystoma was removed, the corpus luteum was not present in it, but was definitely observed in the other ovary. Pregnancy continued uninterrupted, until eight weeks later when the patient was readmitted on account of profuse bleeding from an imminent abortion which had to be completed artificially. The convalescence was uneventful in both of these patients. The tumors may or may not have been factors in causing the abortions, but this seems rather improbable. In the third patient, a therapeutic abortion with sterilization and removal of an ovarian cystoma was done at the end of the second month of pregnancy. The indication for the operation was found in a serious progressive toxic retinitis. The only reason for including this patient is because the tumor was definitely observed to develop during pregnancy and proved to be a corpus luteum cyst.

DISCUSSION

While obviously no sweeping conclusions can be drawn from such a small series, yet a review of them brings up a number of rather interesting points for discussion. The most serious emergency which developed was to be found in torsion of the pedicle of the tumor. This accident occurred in six or 20 per cent, of our 30 cases. This is a much higher incidence than is seen in connection with such tumors in the nonpregnant individual and represents a real menace to the life of the woman. It undoubtedly is a result of the changing position of the tumor as the uterus enlarges with probably some lengthening of the pedicle, so that the tumor becomes more freely movable within the abdomen, instead of lying more or less protected in the pelvis. While these women represented the most serious emergencies encountered, there were possibilities of serious trouble in the 3 patients mentioned where the tumor offered a mechanical obstruction to delivery, but this was avoided by performing cesarean section on two of them and by a lucky manual displacement of the tumor during labor in the third.

Another point of interest is the fact that in 5 cases the tumor very definitely developed during the course of pregnancy and in each instance proved to be a corpus luteum cystoma. This is a matter of some importance and will be mentioned again in connection with therapy.

That group in which operation included removal of the corpus luteum is of particular physiologic interest. In each instance the operation was followed by abortion. These abortions occurred on the fourth, fifth, tenth, and fourteenth days, respectively, after operation. On account of their time intervals it would seem reasonable to suppose that the patients aborted as a result of the removal of the corpus luteum, rather than from any trauma at operation. As a matter of fact, operation involved little or no handling of the uterus at all. This probability is further supported by the fact that in three of these women, death of the ovum had apparently occurred before the abortion took place. It must be recalled, however, that in one of these patients there had been some symptoms of threatened abortion prior to operation. In this instance the removal of the corpus luteum probably precipitated the abortion.

The question naturally arises as to how long the corpus luteum and its hormone, progesterone, are essential for the maintenance of pregnancy in the human female. Unfortunately our present state of knowledge does not permit a specific answer to this question. Many observations by a number of investigators have given us a clear idea as to the relationship of the corpus luteum and its hormone, progesterone, to pregnancy in the experimental animals. Thus, Fränkel's pioneer work showed that removal or destruction of the corpus luteum in the first half of pregnancy in the rabbit resulted in either death of the embryos with resorption or abortion. Allen and Corner succeeded in maintaining pregnancy to term by the administration of corpus luteum hormone in rabbits which were castrated immediately after mating. Snyder has brought about the prolongation of pregnancy in the rabbit by inducing a second ovulation with the development of new corpora lutea in the latter part of pregnancy. From such experiments it is obvious that the corpus luteum and its hormone have a profound influence on pregnancy in this species of animal. In the guinea pig, the removal of the corpora lutea during pregnancy generally results in abortion, but not always, and even when removed in the first half of pregnancy at times no interruption to the pregnancy results.

In the woman, observations at the time of cesarean section at term will in many instances reveal the corpus luteum of that pregnancy as still being present, while in others it cannot be seen and presumably has degenerated some time previously. I have observed similar variations in abdominal hysterotomies at earlier periods of pregnancy, when therapeutic abortion and sterilization was indicated, though not in the first three months. The woman who habitually aborts, presumably aborts on account of premature degeneration of the corpus luteum, and many of these women can be carried through pregnancy successfully by the administration of progesterone for the proper period of time, but it is usually not necessary to continue the therapy to term.

In the 5 patients noted in our series above, all aborted after the removal of the corpus luteum in early pregnancy. This is a common experience and has been noted by many authors. In 2 cases reported by De Lee in 1916 an attempt was made to maintain the pregnancy by transplanting the corpus luteum after its removal, but without success. When abortion does occur after the removal of the corpus luteum, there seems to be little or no doubt that this is the primary causative factor.

On the other hand, this may not be the inevitable result. Thus Ask-Upmark, in a collected series includes 17 examples where bilateral oophorectomy was performed during early pregnancy and yet the pregnancy continued to term. In three of these, the pregnancies were in the first month. In these the corpus luteum obviously must have been removed at the time of operation. More recently, Pratt reported 2 patients

in whom the corpus luteum was apparently removed in the first month of pregnancy and yet both went to term quite normally.

From what has been said, it is apparent that the corpus luteum and its hormone bear an important relationship to pregnancy. It is also apparent that while in general the corpus luteum is necessary for the proper maintenance of pregnancy in the early months, the duration of the time that this necessity exists varies in individuals. Why this should be so, it is impossible to say, but it offers an interesting problem to speculate upon. Ehrhardt in 1934 and McGinty with his coworkers in 1936 have succeeded in recovering appreciable amounts of progestin from the human placenta. Quoting the latter, "While the corpus luteum may not be essential for the continuance of human pregnancy, one cannot conclude that the luteal hormone is dispensable from that observation alone since the placenta may produce its own progestin." If this possibility has any bearing on the situation at all, and one cannot say definitely at present, it again is probably a variable factor both from the standpoint of the time when the placenta acquires the capacity for producing progestin, and the amount that it produces.

Leaving these more or less theoretical considerations, I will discuss briefly the line of procedure to be followed when an ovarian or parovarian tumor is encountered in association with pregnancy. The situation presents serious possibilities and obviously calls for the surgical removal of the tumor. The operation involved is usually a very simple one and is attended by minimal risk on the part of the patient. The question naturally arises as to when this should be done. If discovered during the early months of pregnancy and removed immediately, the patient is of course relieved of all possibility of serious complications developing later in pregnancy or at the time of labor. On the other hand if removal of the tumor includes removal of the corpus luteum, the probability is that abortion will result. Only occasionally, as in the tumor actually known to have developed during pregnancy, and which probably represents a cystic corpus luteum, will we have any suspicion as to whether the tumor contains the corpus luteum or not. On account of this possibility, one would be rather hesitant about urging operation in the early months, but from this standpoint, there is not sufficient evidence available to say exactly when the period of safety has been reached. I would tentatively place it at about the middle of pregnancy, though recognizing the fact that there are probably many variations from this.

Of course in the presence of an acute emergency such as torsion of the pedicle, immediate operation is indicated no matter what the period of pregnancy. In the event that operation involves removal of the corpus luteum, I would offer as a therapeutic suggestion, that the immediate administration of progesterone be begun. I have not had the

opportunity as yet of carrying out such therapy since progesterone became available, but it would appear to be a logical form of therapy to employ.

In the second half of pregnancy operation should be attended by little risk either to the pregnancy or the patient. If, however, the tumor is not discovered or if the patient is not seen until the last month of pregnancy, in most instances the procedure of choice will be to perform cesarean section and at the same time remove the tumor. If the tumor has resulted in a mechanical obstruction at the time of labor, this will of course be the obvious procedure to follow. Finally if the tumor for one reason or another not be removed during pregnancy, operation should be carried out as early in the puerperium as is possible.

SUMMARY AND CONCLUSIONS

Thirty patients with ovarian and parovarian tumors associated with pregnancy are presented. All but two were operated upon with no maternal deaths. In 5 women, where removal of the tumor involved removal of the corpus luteum, abortion occurred in each instance. Abortion occurred in 3 other instances but the accident was apparently not attributable either to the tumor or the operation.

Torsion of the pedicle of the tumor was found to be a frequent complication, occurring in 20 per cent of the patients in the series.

A tumor known to develop during the course of a pregnancy will quite probably prove to be a corpus luteum cystoma.

Suggestions as to the modification of the rules of treatment are presented.

REFERENCES

Allen, W. M., and Corner, G. W.: Proc. Soc. Exper. Biol. & Med. **27**: 403, 1930. *Ask-Upmark, E.:* Acta obst. et gynec. Scandinav. **5**: 211, 1926. *De Lee, J. B.:* Surg. Gynec. Obst. **22**: 80, 1916. *Ehrhardt, K.:* München. med. Wchnschr. **81**: 869, 1934. *Fränkel:* Arch. f. Gynäk. **68**: 438, 1903. *Herrick, E. H.:* Anat. Rec. **39**: 193, 1928. *McGinty, McCullough, and Walter:* Proc. Soc. Exper. Biol. & Med. **34**: 176, 1936. *Pratt, J. P.:* Endocrinology **11**: 195, 1927. *Snyder, Franklin F.:* Bull. Johns Hopkins Hosp. **54**: 1, 1934.

DISCUSSION

DR. CARL H. DAVIS, WILMINGTON, DELAWARE.—Dr. Wilson's experience confirms earlier observations regarding the risk to the pregnancy from too early removal of a cyst developing in the ovary containing the corpus luteum of pregnancy. Obviously acute symptoms from torsion may necessitate prompt surgical removal, but when possible the operation should be postponed until the second trimester is well started. Besides the lessened risk to the pregnancy a considerable percentage of the cysts up to 3 or 4 inches in diameter are temporary corpus luteum cysts which gradually disappear after the first trimester.

The problems associated with diagnosis have caused me greater concern than the question of treatment after a definite diagnosis. A small corpus luteum cyst associated with spotting may be found during the first trimester and one may be uncertain as to whether the patient has an intrauterine or extrauterine pregnancy.

A near tragedy once resulted from my failure to recognize at the time of my original examination that a patient had an ovarian cyst in the midline in front of the uterus. This patient consulted me first on Feb. 20, 1928 stating that her last period had occurred on December 11. At the time of this first examination I found what was believed to be an evenly enlarged uterus the size of a four months' pregnancy. On April 4 she developed a severe right-sided pain, which proved to be due to pyelitis, and on April 27 the uterus was emptied by vaginal hysterotomy. While the mass believed to be the uterus remained too large following the termination of pregnancy her general condition seemed better, and she was permitted to go home. About a week later, however, she was brought back to the hospital with abdominal pain and vomiting, and it was evident that she had an acute abdomen with intestinal obstruction. On opening the abdomen a gangrenous right-sided ovarian tumor 12 by 16 cm. in diameter presented itself. There were several twists of the pedicle and this involved the appendix which was also gangrenous. The tumor and appendix were removed without difficulty. I next explored the culdesac and found a gangrenous loop of intestine. Twenty-five centimeters of the ileum were removed and a lateral anastomosis made. Examination of the specimen indicated that the patient had an old dermoid cyst which had rotated so as to lie on top of the pregnant uterus.

Fortunately the patient made an uneventful recovery and became pregnant again in May, 1930. When examined shortly after missing the first period, a left-sided cyst about 8 cm. in diameter was found. This began to show evidence of a reduction in size near the end of the first trimester, and following delivery, examination indicated that the left ovary was only moderately larger than normal. There was no evidence of cyst formation during a third pregnancy which occurred in January, 1932.

DR. J. L. FRAENKEL, NEW YORK, N. Y.—We are badly in need of a collective study of the comparative physiology of the corpus luteum in all mammals. My scientific friends and pupils, headed by my old assistant Fels, are at work upon this comparative study. In my trip around the world I won many coworkers, each one investigating one animal, from the marsupials in Australia to the viviparous snakes in São Paulo.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—I wish to report a short series of cases from the Methodist Episcopal Hospital. There were 11 complicating ovarian cysts in the last 8,500 deliveries. Delivery was 6 times by cesarean section. Four patients were delivered from below without trouble, the cyst having slipped spontaneously out of the way either before or during labor, or we were able to displace the cyst. One patient who was five months pregnant was operated upon for an ovarian cyst with a twisted pedicle, and later hysterotomy was done for a dead fetus. Another patient was operated upon when four months pregnant for ovarian cyst with a twisted pedicle and was subsequently delivered at term without trouble.

The x-ray helps a great deal in diagnosis. A young woman, thirty years old, was sent to me for operation for an ovarian cyst. On examination I decided it was not an ovarian cyst but a pregnancy of about four months' duration in a thin-walled symmetrical uterus. X-ray demonstrated the fetal bones, although the patient refused to accept the diagnosis. If a dermoid cyst or a pregnancy is suspected there is no better way to make the differential diagnosis than with the x-ray, provided of course the duration of the pregnancy is sixteen weeks or more.

DR. CLARENCE B. INGRAHAM, DENVER, COLO.—I have encountered 13 cases of ovarian tumor during pregnancy. Five were pseudomucinous cystadenomas. Two of these were very large, one being found ruptured postpartum. There were four simple cysts, one parovarian cyst with a twisted pedicle, one serous cystadenoma,

20 pounds in weight and one dermoid. Finally there was a case with a graafian follicle cyst and corpus luteum in the same ovary, included in this group because abortion followed its removal.

Four abortions occurred within the first two months of gestation and two later miscarriages. One abortion occurred prior to the finding of the cyst. The patient with the graafian follicle cyst and corpus luteum in the same ovary was operated upon as an ectopic pregnancy on account of bleeding. Another patient with a corpus luteum removed on the same side as the cyst, two months pregnant, aborted three days after her operation.

Early in pregnancy the lutein-like substance from the placenta may take care of the pregnancy. Petri mentions the case of Essen-Möller who extirpated both ovaries with the corpus luteum, but delivery at term followed 260 days after operation.

I believe it is the consensus of opinion that operation for removal of the tumor is best done after the second month and during the first half of pregnancy. Though operative technic has improved since the time of McKerron's report, I believe his findings are still representative:

MONTH OF PREGNANCY	ABORTIONS EXCLUDING COMPLICATIONS
2	5----18.5%
3	5---- 8.8%
4	3---- 5.3%
5	2---- 6.2%
6	4----22.2%
7	3----20.0%
8	4----57.1%
9	0----00.0%

These figures show that most miscarriages follow operations done in the second half of pregnancy. In the last month of pregnancy, removal of the cyst with cesarean section is indicated, for we would not want a patient to go into labor immediately following an abdominal operation.

DR. JOSEPH B. DE LEE, CHICAGO, ILL.—Years ago when the theory that the corpus luteum preserved pregnancy was first advanced, I applied this principle in two cases. Both patients had ovarian cysts, one being about two and one-half months pregnant and the other not quite four months. The corpus luteum in each case was in the ovary which I had to remove, so I cut out the corpus luteum, split it and planted it in the folds of the broad ligament, hoping thus to prevent an abortion. This had never been done before and not to my knowledge since that time. The results were not happy. One woman aborted within several days. In the other abortion began several hours after the operation, but when I started to clean out the uterus I found it had ballooned out to the size of a six and one-half months' pregnancy and was above the navel. There was an acute paralysis of the uterine wall and the uterus was full of blood.

Paralysis of the uterine wall is not an unknown entity. Buettner of Basel, Switzerland, reported several cases of acute dilatation of the uterus in pregnancy, and it is possible that we might associate this action of the transplanted corpus luteum in this case with the modern theory that it produces a hormone which relaxes the uterus.

DR. RUDOLPH W. HOLMES, CHICAGO, ILL.—In my own experience I had to deal with far more tumors complicating pregnancy during the first half of my practice than in the later years. This difference I have ascribed to the fact that gynecologists have eliminated those ovarian tumors antedating pregnancy by operation.

My first experience with ovarian tumors occurred about 1901. The patient had a cyst of the left ovary larger than the fetal head which had prolapsed into the pelvis, and one of the right ovary the size of a grapefruit. She had been in labor much over twenty-four hours, attended by two general practitioners who were hoping that the tumor would recede, permitting the head to descend. A cesarean section was performed and then both tumors and the tubes were removed. Much to my surprise over a year later I performed a second section, and later the patient had still a third section. It is evident that some of the ovarian cortex must have been left.

When it was believed that the corpus luteum of pregnancy played a vital rôle in preserving the pregnancy, I was accustomed to shell out the corpus luteum if it were in the ovarian tumor and merely drop it into the abdomen. By good fortune or coincidence none of my patients whose tumors were removed early in pregnancy aborted. Such procedure, or the burying of the corpus luteum, should not be done in the event that a papillomatous or ovarian dermoid carries the corpus luteum. Possibly the luteal extracts now on the market may obviate the necessity of considering the retention of the corpus luteum in the event its development were in the tumor.

DR. J. P. PRATT, DETROIT, MICH.—May I say a word about assuming too readily that the corpus luteum is responsible for the prevention of abortion. Several of the patients described had sufficient difficulty before operation to threaten abortion. Some pregnant patients in whom a laparotomy is performed, a gallbladder and appendix or nothing at all is removed, abort following the operation. This certainly does not indicate that the loss of the gallbladder or appendix causes abortion.

Much of our present opinion concerning the progestin mechanism in the human being is a matter of inference from animal experiments. The need for the corpus luteum hormone may not be so great in the human being as would be inferred from animal work.

In one instance I removed a corpus luteum on the twenty-first day after the onset of the last menstruation. The patient had come for sterility, and was operated upon for retroversion and other complicating circumstances. It seemed safe on account of the recent menstruation to remove the corpus luteum for study. The patient did not menstruate in the usual two or three days following the removal of the corpus luteum but continued through a normal pregnancy and lactation. This is, therefore, one clear-cut illustration of a normal pregnancy without the presence of a corpus luteum after the beginning of nidation. Both ovaries had been carefully inspected to insure that no other corpus luteum was present.

DR. WILSON (closing).—Of course, in comparing the conditions in human beings and in animals we get in trouble right away as the time relationships are quite different. In the rabbit, for instance, the pregnancy lasts only thirty days. Destruction of the corpus luteum in the first half of the pregnancy terminates the pregnancy. Of course the rabbit is a very immature animal at birth, and we cannot say that fifteen days of the pregnancy, or half its duration corresponds to a similar time in the woman's pregnancy.

In regard to the therapy I hope sometime to have the opportunity, in a case of torsion of a cyst for instance, with removal of the corpus luteum, of following the operation by the administration of progesterone.

THE THECA, GRANULOSA, LUTEIN CELL TUMORS OF THE HUMAN OVARY AND SIMILAR TUMORS OF THE MOUSE'S OVARY*

HERBERT F. TRAUT, M.D., AND J. S. BUTTERWORTH, M.M.,
NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, and the Department of Pathology, Cornell University Medical College and New York Hospital)

THE process of accumulating knowledge concerning neoplastic growths falls quite naturally into different phases. Among these the most important are the clinical description of patients harboring the growth, the histologic study of the tumor, investigation of its embryologic background, physiologic studies of it, and finally, its biologic evaluation. Studied in these various ways, tumors yield many of the important facts which the physician must possess. However, it is rarely possible to apply all these methods of attack to a given type of tumor or group of tumors, either because we do not know how to apply them or because the tissues in question do not adapt themselves to one or another of the modes of study. In the theca, granulosa, lutein cell group of neoplasms, we have an unusual opportunity to acquire information, because all the procedures mentioned are applicable. These tumors present definite clinical evidence of their presence by the symptoms they produce; their histologic aspects are characteristic; study of their embryologic background yields most helpful information; they are physiologically active because they secrete hormones which influence other tissue in ways we can evaluate; and finally, we have learned how to produce them in a laboratory animal so that they may be studied not only in every phase of development, but also as frequently as we desire. Therefore, this group of tumors presents an unusually fertile field for study and one in which great strides toward understanding have been made.

A study of the literature concerning these tumors indicates that the first contribution was made by Rokitansky in 1859 when he described a lobulated tumor the size of a child's head in the left ovary of a woman aged sixty-five. This tumor was composed entirely of lutein cells containing much lipoid material. A little later, in 1882, Maffucci recorded the details of a similar tumor, excepting that the lutein cells were not so predominant, there being granulosa cells as well as theca cells present in large numbers.

Von Kahlden, in 1895, gave the first unmistakable description of a granulosa cell tumor and named it "graafian follicle adenoma." This announcement of a new type of tumor attracted wide attention, so that in the years following, many other granulosa tumors were recognized and described. It was soon learned that these

*Read at a meeting of the Brooklyn Gynecological Society, April 2, 1937.

neoplasms could assume a great variety of forms so that nothing approaching a classification of them was possible until 1915 when Robert Meyer published his monograph on the subject. However, in 1931, Moulonguet and Dobkevitch published the work of their teacher, Lecéne, who apparently had long before recognized a luteinized type of granulosa cell tumor, had collected and studied several specimens, and had named them "folliculome lipidique." It was not until 1932 that the last member of this interesting group of tumors was reported by Loeffler and Priesel to which they gave the name of "fibroma theca cellulare xanthomatodes ovarii," more commonly known as the theca cell tumor.

Thus the discovery and collection of data concerning this family of neoplasms have already covered many years. There still remains much to be done, as the lutein tumors and theca tumors are somewhat rare. However, a great step has been taken to shorten the process, for Furth and Butterworth have discovered a method whereby the granulosa and lutein tumors can be produced in large numbers in the experimental animal. In a series of studies on experimentally induced leucemia, they discovered that a considerable percentage of their radiated mice developed these ovarian tumors. This abundant source of material makes it possible to examine more completely all stages of growth and to determine more accurately interrelationships between them, as well as to study their origins.

It is the purpose of this paper to summarize our knowledge of the human tumors in some detail and to draw conclusions concerning them through comparison with what has been observed in the mouse tumors.

CLINICAL DATA CONCERNING THE HUMAN TUMORS

The theca cell tumors would seem to be somewhat rare, as only about twenty-three such tumors have been reported. However, they are probably of much more frequent occurrence than this would indicate for, as will be noted when their histology is discussed, they are difficult of recognition, particularly in the unluteinized (undifferentiated) forms. Granulosa cell tumors are much more common. Schröder estimates that they constitute from 2 to 3 per cent of all solid ovarian tumors, while Von Szathmary found 9 in a series of 203 solid tumors, or an incidence of 4.4 per cent. The luteoma, like the thecoma, is also a rare tumor because, though easily recognized, only twelve have been recorded in the literature. However, partially luteinized granulosa cell tumors are much more common. The age incidence can be given with some degree of definiteness with regard to the granulosa tumors. They are most commonly found in women over forty years of age, although occasional examples are seen in younger women between puberty and the menopause, and a few in children. The luteomas were all seen in mature women ranging from twenty-one years to sixty-five years of age, while all excepting four of the thecomas have been found beyond the menopause.

SYMPTOMATOLOGY

The clinical history of patients having one of these tumors depends primarily upon the fact that they possess endocrine activity, while mechanical and circulatory disturbances, and occasional malignancy, are accessory factors. The hypersecretion of estrin by the theca, granulosa, and probably also by the lutein cell tumors produces a characteristic syndrome associated with hyperplasia of the endometrium, irregular uterine bleeding and gradual symmetrical hypertrophy of the musculature of the uterus. In the prepubertal female, luteomas and thecomas do not occur; therefore, precocious development of the secondary sex characters and uterine bleeding are seen associated only with the granulosa tumor, or with tumors outside the ovary, such as those of the adrenal and prepituitary gland.

After the menopause there is a recurrence of a more or less regular type of uterine bleeding, enlargement of the atrophic uterus and occasionally a recrudescence of sex desire. Infrequently breast atrophy is replaced by transitory hyperplasia. Curettage of the uterus reveals a cystic glandular hyperplasia of the endometrium in the majority of patients; however, a few instances have been reported in which the premenstrual or secretory type of endometrium was seen, even in women of advanced age.

During the period of sexual activity, the symptomatology due to the endocrinal potencies of the tumors is less noticeable because of the proximity of normal menstrual function and also because the other ovary which is often normal may serve to mask the picture. However, there is usually a period of amenorrhea followed by menorrhagia or metrorrhagia, or there may be simply irregularity of the menses.

If the tumor is benign, its removal serves to reestablish the former status of the patient, thus giving clinical proof of its endocrinal activity, excepting that in those prepubertal cases where the menarche is imminent, the individual may continue sexual development with more or less normal periodicity of the menstrual function.

Approximately 80 per cent of the granulosa tumors are clinically benign. When malignant, they metastasize rapidly and produce death in a short time. Only one case of malignant theca cell tumor has been reported, while the luteomas are probably more frequently in this category, as three of the twelve tumors reported have been interpreted in this way.

Nothing is known concerning the radiosensitivity of thecomas and luteomas. Although, judging from the effects of radiation upon the normal theca and lutein cells of the mouse, it would seem that they were most radio-resistant. All observers with few exceptions agree that the malignant granulosa cells are extremely sensitive to radiation therapy. As we shall show in the mouse's ovary, x-rays at first depress

and then subsequently stimulate the growth of granulosa cells to such a degree that tumor formation results. It is interesting to note reports in the literature of a number of patients who developed granulosa cell tumors following heavy radiation. The cases of Vogt, Smith, and an unpublished case at the Memorial Hospital are examples of this type of reaction in the woman.

HORMONAL EFFECTS OF THE THECA, GRANULOSA, AND LUTEIN CELL TUMORS

As has been mentioned, the predominant effect of these tumors so far as we are now able to judge is upon the uterus and breast, with some influence upon the secondary sex characteristics. This seems to be due to the secretion of estrin, because prolonged injection of large amounts of estrin in the experimental animal can be shown to produce exactly analogous phenomena in the uterus and its endometrium.

However, very exceptionally, so-called granulosa cell tumors may be associated with a secretory (premenstrual) type of endometrium. It would seem probable, therefore, that occasionally some luteinization takes place in such cases, so that progestin also becomes a product of the tumor (folliculome lipidique of Lecéne). Biologic proof of this deduction is lacking, so that it is based only upon histologic evidence and must, therefore, be viewed with reserve.

The effect of luteomas on the endometrium is obscure because only a few tumors of this type have been reported, and none has been described specifically as to its effect on the endometrium. The clinical histories, however, speak chiefly of an amenorrhea with the exception of Wolfe's case, a young woman of twenty-one years, who showed menstrual irregularity. As we shall see in the mouse luteomas, the effect on the endometrium is mainly a proliferative one, only occasional secretory activity having been induced.

Curiously enough, one seldom sees fibromyomas of the uterus or chronic cystic mastitis associated with the hyperestrinism induced by granulosa cell tumors. If the theories of Witherspoon and those of Geschickter and Lewis be true, one might expect to find some increased evidence of these pathologic conditions associated with granulosa or theca cell tumors, especially in the premenopausal group of patients.

The secondary sex characteristics usually are predominantly feminine in patients harboring one of these tumors, and as has been noted, they may be called forth prematurely in the young. However, a few instances of masculinization are to be noted as exceptions, such as the case of luteoma reported by Cosacesco, and an unreported case of granulosa cell tumor in Studdiford's experience. In these patients, masculine hair distribution, excessive beard growth, coarsening of the facial features, deepening of the voice, amenorrhea, and penile hypertrophy of the clitoris were seen. Clinically a preoperative diagnosis of arrhenoblastoma was justifiable in these patients, and yet the tumor

of the ovary in each case showed respectively a luteoma and a granulosa cell tumor. The hormonology of these aberrant cases is not clear at the present time, but it seems quite probable that there may have been some adenomatous elements of the adrenal cortex in the ovarian tumors or the adrenal gland itself.

PROOF OF HORMONAL ACTIVITY

Siebke and Schuschiana, Frank, Pahl, Neuman, Melnick and Kanter, and Spielman have presented a convincing mass of experimental proof that the blood of patients with granulosa cell and theca cell tumors contains increased amounts of estrin. Furthermore, it has been shown that the tumors themselves, and particularly the thecoma, contain the substance in large amounts. The investigations seem to indicate that, although these tumors do not excrete excessively large amounts of estrin, the secondary hormonal effects are in all probability produced by its long-continued and constant action, on the one hand; and on the other, that there is no opposed corpus luteum effect in most cases. Further studies along these lines are much needed, particularly in connection with the luteinized types of granulosa tumors such as described by Maffucci, Plate and Lecéne, and also the true luteoma.

HISTOLOGIC ASPECTS

The gross pathologic characteristics of these tumors are so varied as to defy description. However, in general it may be said that the thecomas tend to simulate fibromas of the ovary in size, shape, and consistency. The cut surface also bears out this resemblance with the exception that the white fibrous whorls of tissue may be flecked or streaked with yellowish areas. This color is due to the carrotin contained in the theca cells.

The granulosa tumors are more versatile in their gross manifestations. They may be smooth or lobulated in surface contour and are frequently semisolid or cystic; cyst formation depends upon the type of tumor differentiation, the folliculomas being more soft and cystic than other forms. The larger tumors tend to necrosis so they may be quite soft and contain degenerative cyst cavities. The coloration of the cut surface is yellowish gray with a marked frequency of hemorrhagic discoloration of the cystic areas. About 10 per cent are bilateral. The luteomas are more often solid than cystic and are not noted as being of large size. Their cut surfaces display a homogeneous yellow matrix of cellular tissue.

Theca tumors appear microscopically as fibromas in which islands of fusiform cells occur. These cells are arranged in a basket weave pattern and are characterized by the intracellular fibrils which serve to differentiate them from the ordinary ovarian stroma cell. They are possessed of an elongated nucleus which is quite uniform in size.

Mitoses are not seen. They tend to differentiate from the mesenchymal type of connective tissue cell in an epithelial direction. In doing this, they retain the intracellular collagen fibrils but tend to increase in size slightly and develop an increased tendency to stain with fat stains because of the appearance of cholesterol esters within the cells. This change presumably is somewhat analogous to the change seen in some granulosa cell tumors when they undergo luteinization. There are, therefore, two distinct types of theca cells with regard to the degree of differentiation: the luteinized, which form is easily recognized because these cells stand out clearly from the connective tissue background; and the unluteinized, which is more difficult of recognition, and in all probability is not identified histologically in its true relationship by the majority of pathologists.

The granulosa cell tumors offer much less difficulty in diagnosis than the thecomas, because they are far better known. However, they assume such a variety of cell arrangements, as well as different degrees of cellular differentiation, that some space should be devoted to a detailed description of them.

The granulosa cells, themselves, resemble the cells lining the normal graafian follicle. They have a small oval or round nucleus which takes the hematoxylin and other basic stains intensely. This is surrounded by a scanty cytoplasm which is very faintly acidophilic. The cells are uniform in size; their shape, however, varies with their environment, assuming almost any form necessary for accommodation to a given space. They vary also with their degree of differentiation from cells such as those seen in the primordial graafian follicle to the hypertrophic, pale and fat laden cell seen in the lutein stage. In the latter phase, the cells contain phospholipoids and respond to specific fat stains. Call-Exner bodies consisting of a radiating rosette of granulosa cells about a small acinus, the latter containing hyalinized fragments of cellular débris, are often seen and are quite pathognomonic when present. Aside from the variations in the cells themselves, groups of cells show marked versatility in the patterns they describe. The following constitute the most striking types of organization:

1. Folliculoid arrangement of the cells into small or large acini surrounded by a margin of granulosa cells resembling in some degree at least the normal graafian follicle, is the most common and probably represents the best differentiated form of the tumor. The theca interna may be scant or absent. The central cavity contains liquor folliculi into which, not infrequently, hemorrhage has taken place

2. Other tumors display a cylindromatous arrangement of dense columns of cells separated by fibrous connective tissue. There is little or no cyst formation. This may be considered a less differentiated form of the tumor than the folliculoma. When partial luteinization has occurred, and particularly when the columns of cells are widely separated by connective tissue stroma, these tumors have been mistaken histologically for Brenner tumors until specific stains were applied to distinguish the fundamental difference in the nature of the cells.

3. Still other tumors show a tendency on the part of the granulosa elements to dispose themselves between planes of connective tissue forming tongue-like processes or trabeculae, seldom growing into solid sheets or cylinders of cells. This is usually a diffuse sort of growth and is the least differentiated pattern, although the cells, themselves, may appear to be quite adult and well formed.

4. Rarely the granulosa cells form a system of tubules in which single rows of cells arrange themselves about a central acinus as though it were a duct. Such an arrangement of cells might be thought to be related to some form of tubular adenoma, such as Pick's testicular tumor, were it not that one can usually prove beyond doubt that they are true granulosa cells.

The connective tissue elements, particularly in the trabecular forms, are very vascular. In the follicular variety the connective tissue yields a basement membrane which at times closely resembles theca interna, but for the most part is compressed and partially or completely hyalinized. Occasionally fibrous connective tissue forms the bulk of the tumor with only scant infiltration or small isolated areas of granulosa cell development.

Not infrequently one finds several of the above varieties of arrangement of the granulosa and connective tissue in different portions of the same tumor, indicating presumably different stages of growth or of differentiation.

Apparently any variety of granulosa cell tumor and many theca cell tumors undergo luteinization. Attention to this somewhat uncommon finding was first directed by the teachings of Lecéne who, in the case of the granulosa tumor, gave it the name of "folliculome lipidique." This change is accompanied by a loss of the dense basophilia characteristic of the granulosa cell tumor, some increase in the size of the cell and shrinkage of the nucleus. These cells and the connective tissue about them contain phospholipoids and consequently take the various fat stains quite densely.

Whether a human granulosa cell tumor can become completely luteinized to form a luteoma remains an open question. That this occurs in a mouse tumor there can be no doubt, as will be described presently. However, several partially luteinized tumors such as those described by Lecéne have been reported.

The luteoma, therefore, may develop de novo from other lutein cells, as has been believed. However, this seems unlikely, because mitoses and other evidences of young lutein cells are rare in these tumors. The lutein cells are usually quite uniform in size and have a clear "ground glass" type of cytoplasm which stains only slightly with acid stains. The cytoplasm is abundant with definite cell outline, showing a "mosaic" or "flagstone" pattern. The nucleus is small and eccentrically placed. In several tumors small cells have been described which have a more opaque and slightly basophilic cytoplasm as well as a larger nucleus. It would seem that these are granulosa cells which have not completely undergone the lutein change. The relationship

of the lutein cells to the blood vessels is a very intimate one in which the cells are often seen to be grouped about the blood vessel in a definite perivascular arrangement. Fat stains show the clear cells to be heavily laden with fat droplets.

HISTOGENESIS OF THE THECA, GRANULOSA AND LUTEIN CELL TUMORS

Our knowledge of the antecedent cells from which these tumors are derived is somewhat incomplete. Due to the difficulties surrounding

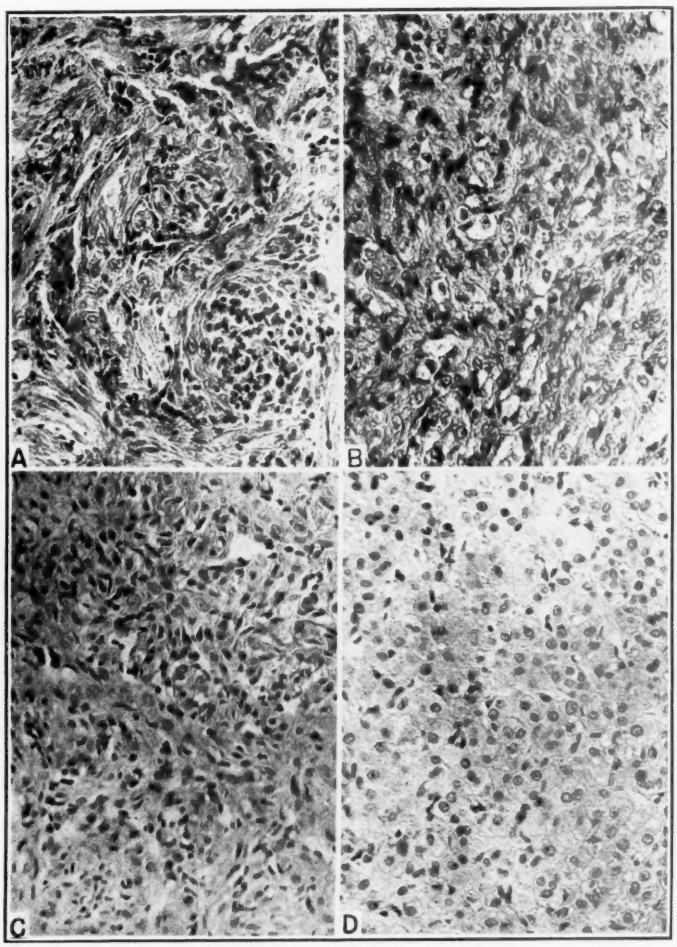

Fig. 1.—Theca tumors. *A*, Thecoma of mouse's ovary showing only moderate differentiation and no luteinization. *B*, A better differentiated tumor from human ovary showing a few luteinized cells. *C*, A human theca cell tumor with an even representation of luteinized and unluteinized cells. *D*, Complete luteinization in a human thecoma.

the absolute identification of cells in the embryonic ovary, as well as the complexity of the cytologic changes taking place in rapid succession, some differences of opinion and misconception have arisen. For many years following the teachings of Pflüger (1863) and Waldeyer (1870),

it was thought that the granulosa as well as the primitive ova were derived from the coelomic epithelium covering the surface of the ovary. A process of down growth of this epithelium in cords to form the so-called Pflüger tubules has been described by many students of the fetal ovary. That at times there are proliferations of the germinal epithelium to support such a theory seems undoubted. However, more

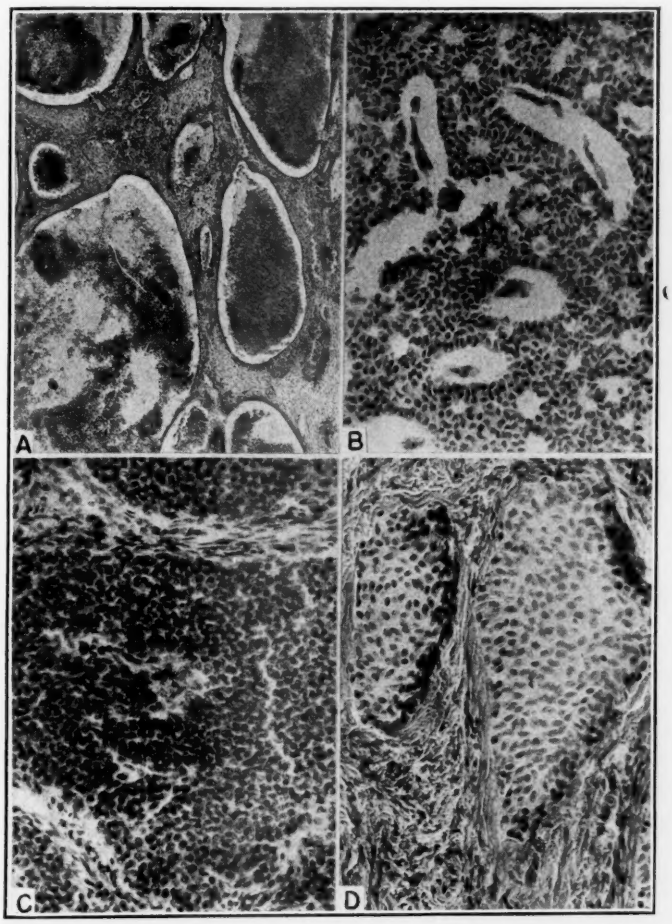

Fig. 2.—Granulosa tumors of human ovary. *A*, Typical *"folliculoma"* arrangement; each acinus is lined by granulosa cells, and contains liquor folliculi and often some blood cells. *B*, A *solid arrangement* with many small follicles, the small ones being "Call and Exner" bodies. This is less well differentiated than the "folliculoma." *C*, *Cylindroma* arrangement. Still less differentiated. Solid columns of cells split up by connective tissue septa. *D*, An unusual *cylindroma* showing early lutein change, simulating a Brenner tumor.

recently, principally through the influence of the Viennese embryologists, under Fischel's guidance, a different explanation of the origin of the theca, granulosa, and ova has come to be understood and at least partially accepted. According to the Fischel school, it now seems very probable that the germinal epithelium contributes nothing to the

formation of the graafian follicle. The primordial sex cells are thought to be derived from coelomic epithelium at some distance from the gonad and to migrate into it during early fetal life. After the arrival of the sex cells, and under their influence, the primitive mesenchymal stroma of the ovary undergoes a series of changes which surrounds each sex cell with an envelope of primitive granulosa and theca cells.

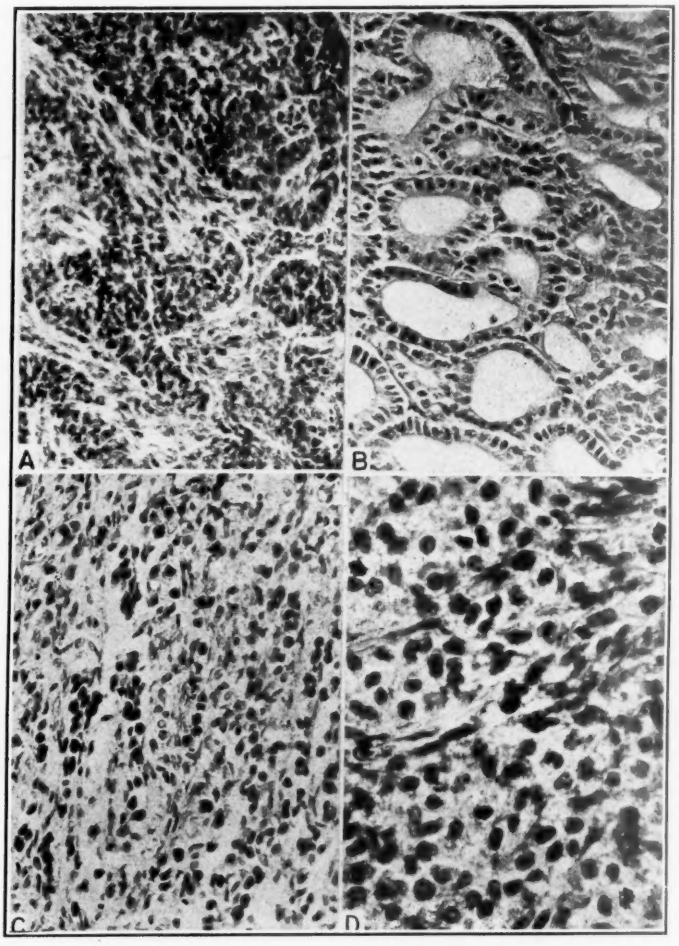

Fig. 3.—Granulosa tumors of the human ovary. *A, Trabecular* arrangement. A common picture in rapidly growing tumors. *B, Tubular* arrangement, which is quite rare. Unquestionably granulosa, but simulating Pick's tubular adenoma. *C, Sarcomatoid* arrangement. Benign, but with few granulosa cells scattered among the connective tissue stroma cells. Patient alive and well six years after operation. *D, Granulosa cell carcinoma,* malignant. Note mitotic figures. Patient died with metastases from this tumor, three months after operation.

If the Fischel concept be true, then the tumors of the granulosal series with their varied cellular content and pattern are mesenchymal instead of mesodermal in origin and are, therefore, more readily understandable.

It has also been generally accepted that the tumors we are considering did not arise in the human ovary from normally differentiated theca, granulosa, or lutein cells. Instead, it has been thought, following the teachings of Robert Meyer and Walthard, that they were formed from unused nests of partially differentiated cells called "Granulosaballen" surviving the period of embryonic development.

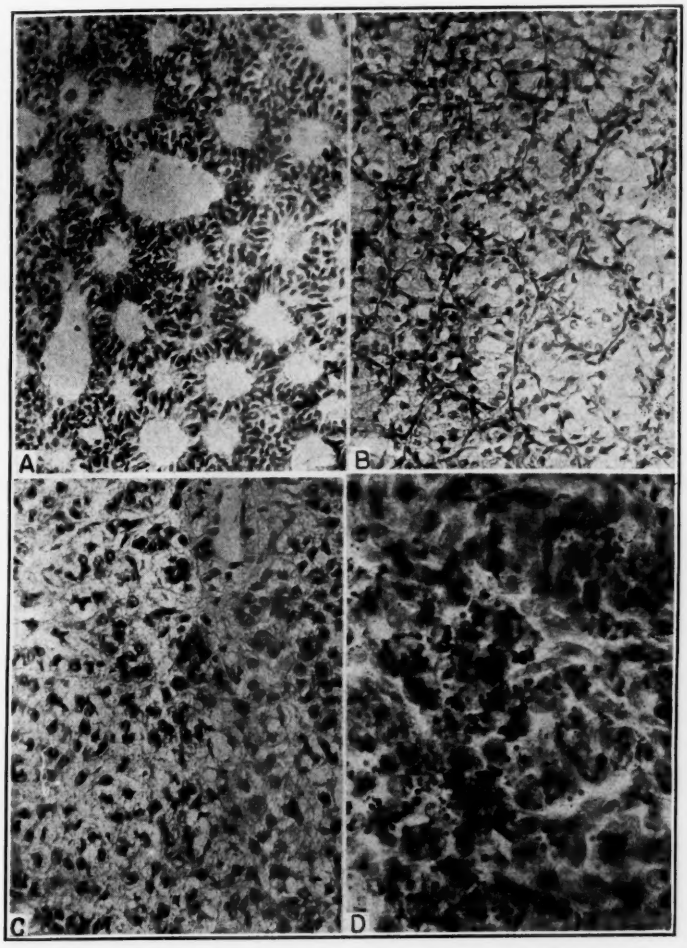

Fig. 4.—*Lutein tumors of the human ovary. A,* Partially luteinized granulosa tumor (diffuse type of Lecéne). *B,* Completely luteinized portion of a granulosa tumor (general type of Lecéne—folliculome lipidique). *C,* So-called "luteoma." Certainly an ovarian tumor of lutein cells, but in all probability a luteinized granulosa tumor. Occasional granulosa cells are still seen. *D,* Luteinized tumor stained with Sudan III to demonstrate intra- and extracellular fat droplets.

These "Granulosaballen" or "Granulosaschläuche" are frequently seen at the hilus of the fetal ovary and occasionally in the ovaries of children. Only a few instances have been reported in which they have been observed in the adult ovary, and none in that of the postmenopausal woman. This explanation of the etiology of tumors most of

which occur in individuals over forty years of age is not very satisfactory, even from a theoretical point of view.

As will be shown later in the irradiated ovary of the mouse, although the changes that occur are not entirely comparable to what takes place in the human ovary and are therefore only suggestive, the granulosa tumors are derived from surviving granulosa cells of the fully differ-

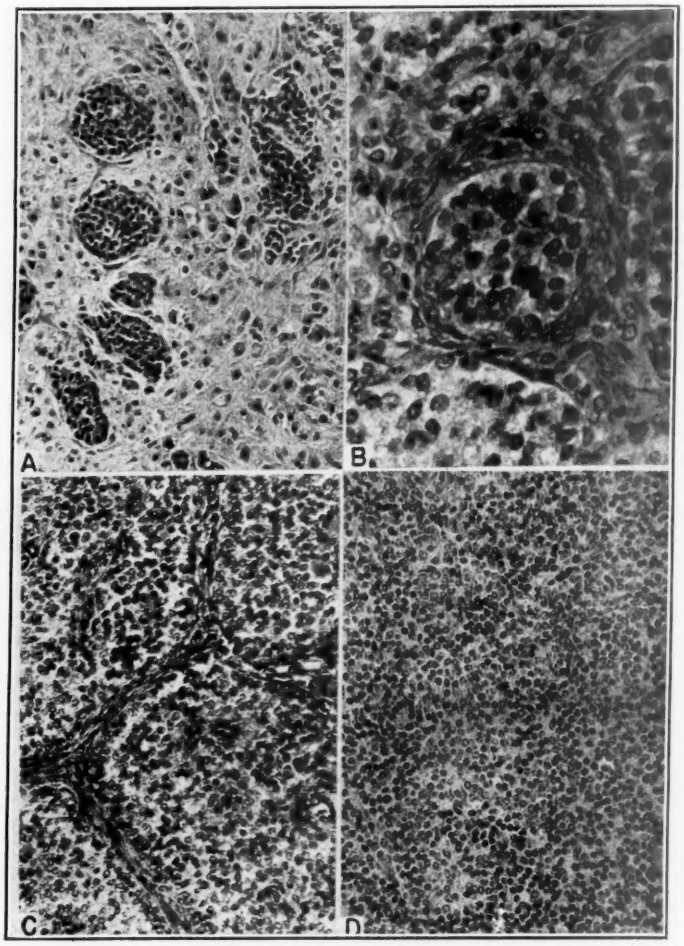

Fig. 5.—Granulosa tumors of the mouse ovary. *A*, Very early granulosa growth after irradiation with x-ray, showing growth among degenerated granulosa, theca and lutein cells. *B*, Later stage of growth showing proliferation of granulosa cells in cylindromatous pattern. *C*, Much later, large cylinders of solid cells. *D*, Solid pattern, no differentiation.

entiated adult ovary. Furthermore, the luteomas are formed by luteinization of the granulosa tumors thus produced. The possibility, therefore, suggests itself that even in the human being, some granulosa cells of the follicular system may survive the menopause and under some unknown stimulus develop into tumors. Or it may be that the

granulosa tumors in the postmenopausal woman have a prolonged growth period and that they commence to grow at or about the climacterium, finally developing to considerable size only at a very much later period.

GRANULOSA CELL AND LUTEIN CELL TUMORS IN MICE

Much is to be learned of the interrelationship of these tumors by a study of experimentally produced ovarian tumors in mice. Several

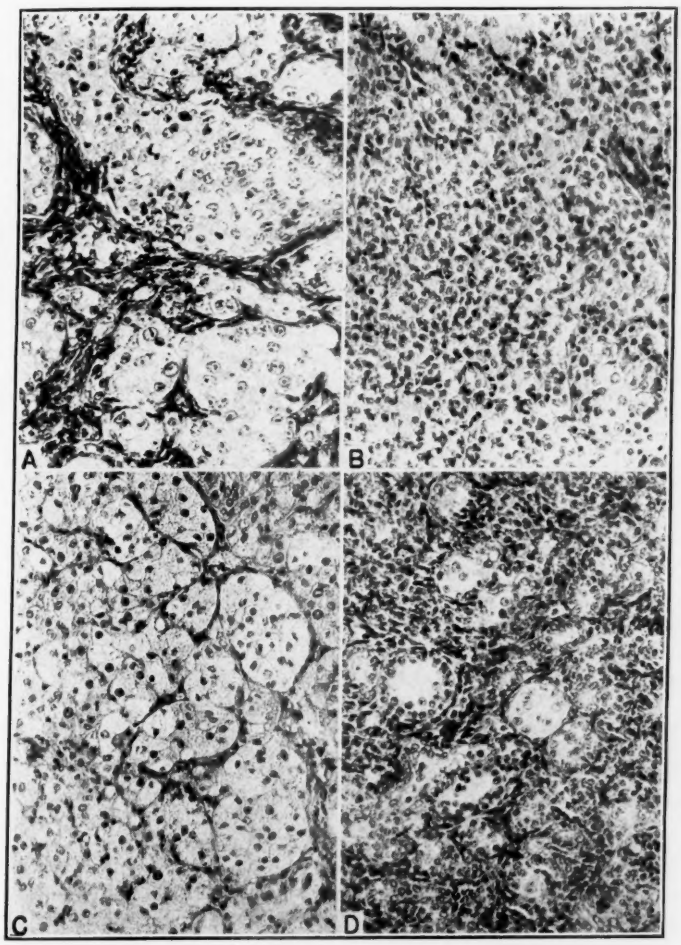

Fig. 6.—*Lutein tumors of the mouse ovary. A,* Localized luteinization with some degeneration in a cylindromatous granulosa tumor. *B,* Diffuse luteinization in a solid type of granulosa tumor. *C,* Compare with Fig. 4, *B.* This is a luteinized granulosa tumor in the mouse. *D,* Granulosa tumor showing tubular arrangement with very early luteinization.

allusions to our findings in these growths have already been made in various connections. However, it seems necessary to give these in a more complete and logical manner, as an understanding of the human tumors is immeasurably helped thereby.

Furth and Butterworth have recently reported a series of 57 ovarian tumors which they induced by exposing sexually mature female mice to 190 kilo., 30 ma. of x-ray radiation at 50 cm. distance through 0.5 mm. of copper plus 1 mm. of aluminum filtration. These animals were allowed to live to senescence and died of relatively natural causes. Thus the period of growth of the tumor following radiation was of various durations. Another series of 65 mature animals has been studied by sacrificing them at progressively increasing periods of time following radiation. The postradiational time varied in this group from 3 to 787 days. Both series of tumors will be described in greater detail in other papers. Dr. Furth has very kindly allowed us to study and make photographs of this large material, a privilege which is very gratefully acknowledged.

A study of the first group of ovarian tumors at once revealed a striking resemblance not only morphologically but from an endocrinologic point of view as well, to the various forms of tumors seen in the granulosal series in the human being, with the exception of the theca cell tumor. The mode of development of these new growths and an interpretation of their origin and relationship is possible only in the second series in which the ovarian changes were graduated as to time interval after irradiation.

CHANGES IN THE MOUSE'S OVARY FOLLOWING X-RAY RADIATION

In general it may be said that the reaction of the cells of the ovary to radiation depends upon their degree of maturity, on the one hand, and their degree of differentiation, on the other. A few of the animals were not quite mature sexually at the time of radiation. In these animals the effect of the rays was more depressing to all cells than in the older animals. In the sexually immature mice, the ovary was reduced to a fibromatous atrophic organ with no surviving epithelium or differentiated stroma excepting the peripheral ovarian epithelium. In the mature animals the ova were the first cells to degenerate and were followed more or less completely by the granulosa, while the theca cells, germinal epithelium, and lutein cells withstood radiation to the extent of survival. The lutein cells degenerate very slowly and show only slight signs of proliferation, whereas, in the granulosa and germinal epithelium, subsequent proliferation is tremendous.

It may be said, therefore, that the radiation effect produces (1) degeneration of all ova; (2) partial degeneration of the granulosa; (3) only slight effect on the theca and lutein cells; and (4) stimulates proliferation of the germinal epithelium and the granulosa cells. The degenerative phase lasts about 150 days after which the proliferative phenomena occur on the part of the granulosa and germinal epithelium.

The proliferation of the germinal epithelium takes place at first on the periphery of the ovary and subsequently produces invaginations

into the substance of the ovary toward the hilum which, if the animal lives 300 to 400 postradiational days, develop into a form of germinal epithelial adenoma which has no hormonal significance and no relation to the granulosa series of tumors. That there is no connection between the proliferation of the surface epithelium and the subsequent development of the granulosal or lutein type of tumor is a conclusion that is reached after careful study of many sections of these tumors. Special thought was given this point because of the Pflüger-Waldeyer theory of the origin of granulosa cells and because of the conclusions of Bramwell, Parkes and Fielding who, in studying infantile animals after radiation, thought that there was such a relationship. In these series of sexually mature animals no definite relationship was found to exist.

The development of the granulosa and lutein tumors took place from surviving granulosa cells and perhaps from theca cells.

The nests of growing granulosa cells can be seen proliferating in the acinus of the partially degenerated follicle. In some the growth is rapid, forming a solid mass of cells similar in every way to the cylindromatous type in the human tumor. In others a small rosette arrangement with a small central area of degeneration simulates the Call and Exner bodies. Occasionally the degeneration of the central area is more complete, the cells being replaced by fluid corresponding to the *folliculoma* type of growth seen in the human tumors. In other areas the proliferation of cells extends in the connective tissue planes and results in a trabecular disposition of the tumor.

Luteinization occurs diffusely as in the Lecéne type of tumor and also in massive foci forming true luteomas. Finally, even the rare tubular arrangement of the granulosa cells was seen in these mouse tumors.

EVIDENCE OF ENDOCRINE ACTIVITY IN MOUSE GRANULOSA TUMORS

It is a well-recognized principle among pathologists that morphologic analogy is not sufficient evidence to establish identity. Therefore, physiologic activity may give important additional evidence to establish the similarity of the mouse to the human tumor. There is every reason to believe that the granulosa cell tumors which develop after radiation in the mouse's ovaries are, if not identical, at least very similar to the human tumors. This conclusion is based upon morphologic similarities and the fact that the uterus, especially the endometrium, reacts to their presence by developing a hyperplastic endometrium. In one animal the uterine wall was penetrated by the endometrium and true adenomyosis was observed.

The luteomas were possibly somewhat more usually associated with the hyperplastic phenomenon in the uterus than the granulosa cell tumors. At first this may seem contrary to what is usually seen in human tumors. However, if one compares the relatively short dura-

tion of these growths in the mouse to that probably obtaining in the woman, it may be supposed that the hyperplasia was the result of the fully mature granulosa cell bodies which then further differentiated to form lutein cells with continued estrin secretion. No unquestionable secretory phase was seen with any granulosa tumor in mice, and only a few luteomas produced this progestin effect in the endometrium.

SUMMARY

Theca cell, granulosa cell, and lutein cell tumors are closely related etiologically and physiologically.

Each of these types of tumors possesses the capability of assuming a variety of growth forms and degrees of cellular differentiation. The theca cell tumor exists in two forms: unluteinized and luteinized, the latter being the one commonly described. In its luteinized form it resembles the diffuse type of luteinized granulosa cell tumor in which there is much fibrous connective tissue. The luteinized granulosa cell tumor in which the cells are closely packed with little intervening fibrous connective tissue has close morphologic resemblance to the luteoma and is probably the only way in which true luteoma can arise, as we have seen only slight evidence of growth in lutein cells. They all secrete estrin and have a similar physiologic effect on the uterus. Whether in addition, the luteinized forms secrete progestin has not been proved. The secretory endometrium reported to have accompanied some granulosa cell tumors as well as the prolonged amenorrhea associated with most of the luteomata strongly suggests that progestin is secreted by these tumors under certain conditions.

The ultimate etiology of these tumors is still in doubt. Whether they are derivatives of coelomic epithelium or whether they come from ovarian mesenchyme remains to be proved. However, the evidence for a coelomic epithelial origin becomes progressively weaker as new information is brought to bear upon the subject.

The belief that the tumors cannot arise from surviving adult granulosal cells is also in doubt. The evidence from our mouse tumors, though not conclusive, points definitely to the possibility that they may arise in this way. Thus the "Granulosaballen" theory of Robert Meyer is placed in greater doubt than has formerly been the case.

That the granulosa cell tumor can become luteinized either diffusely or locally has been demonstrated. This process occurs and explains satisfactorily the occurrence of the Lecéne type of tumor and probably the luteoma as well.

With more careful hormonal studies and examinations of the endometrium in patients carrying luteomas and partially luteinized granulosa tumors, we should expect to find more frequent evidence of progestin activity.

In view of this work which definitely demonstrates that the x-ray ultimately has a stimulating effect upon the granulosa cells, it may be wise to limit the use of x-ray in the woman to those conditions of such urgency as would justify its use despite this effect. It would seem that x-ray abortion and sterilization were examples of procedures which usually would not have this justification.

The studies of the ovarian tumors of mice have been supported by a grant from the International Cancer Research Foundation.

REFERENCES

Theca Cell Tumors: Brosig, W.: Frankfurter Ztschr. f. Path. **49:** 376, 1936. *Geist, S. H.:* Am. J. Obst. & Gynec. **30:** 480 and 650, 1935. *King, E. S. J.:* Austral. & N. Zeal. J. Surg. **1:** 28, 1931. *Loeffler, E., and Priesel, A.:* Beitr. z. path. Anat. u. allg. Path. **90:** 199, 1932. *Melnick, P. J. and Kanter, A. E.:* Am. J. Obst. & Gynec. **27:** 41, 1934. *Neumann, H. O.:* Arch. f. Gynäk. **136:** 556, 1929.

Granulosa Cell Tumors: Abrahamer, I.: Zentralbl. f. allg. Path. u. path. Anat. **53:** 310, 1932. *Babes, A.:* Arch. f. Gynäk. **131:** 45, 1927. *Benda, R., and Kraus, E. J.:* Arch. f. Gynäk. **157:** 400, 1934. *Bland, P. B., and Goldstein, L.:* Am. J. Obst. & Gynec. **28:** 596, 1934. *Fauvet, E.:* Zentralbl. f. Gynäk. **56:** 3088, 1932. *Furth, J., and Butterworth, J. S.:* Am. J. Cancer **28:** 66, 1936. *Klaften, E.:* Arch. f. Gynäk. **150:** 643, 1932. *Küstner, H.:* Zentralbl. f. Gynäk. **56:** 2963, 1932. *Meyer, R.:* Arch. f. Gynäk. **145:** 2, 1931; Ztschr. f. Geburtsh. u. Gynäk. **101:** 800, 1932; Arch. f. Gynäk. **148:** 541, 1932. *Moulonguat, P., and Varangot, J.:* Presse méd. **92:** 1848, 1936. *Neumann, H. O.:* Arch. f. Gynäk. **126:** 553, 1925. *Novak, E.:* Am. J. Obst. & Gynec. **26:** 505, 1933. *Pahl, J.:* Arch. f. Gynäk. **147:** 736, 1931. *Plate, W. P.:* Ibid. **153:** 318, 1933. *Schiller, W.:* Pathologie u. Klinik der Granulosatumoren. Wien, Mandrich, 1934. *Schuschania, P.:* Zentralbl. f. Gynäk. **54:** 1924, 1930. *Shiffmann, J.:* Arch. f. Gynäk. **150:** 159, 1932. *von Szathmary, Z.:* Ibid. **153:** 127, 1933.

Luteomata: Aschner, B.: Arch. f. Gynäk. **115:** 350, 1922. *Bingel, A.:* Deutsche med. Wchnschr. **50:** 330, 1924. *Casacesco-Draganesco:* Presse méd. **39:** 1264, 1931. *Cattaneo, L.:* Berlin Gynäk.-Ref. **14:** 749, 1928. *Cutler, O. L.:* Am. J. Obst. & Gynec. **30:** 131, 1935. *Glynn, E.:* J. Obst. & Gynaec. Brit. Emp. **28:** 23, 1921. *Gordon, A. K.:* Brit. M. J. **2:** 495, 1919. *Grouzdew, V.:* Arch. f. Gynäk. **70:** 445, 1903. *Kermauner:* Stoeckels Handbuch. **7:** 346, 1932. *McIntyre, D.:* J. Obst. & Gynaec. Brit. Emp. **38:** 307, 1931. *Markovitch, M.:* Contribution a l'etude des tumeurs de l'ovaire a cellules Luteiniques, These de Montpellier, 1913. *Moulouguet, P., and Dobkevitch, S.:* Les diagnostics anatomocliniques de P. Lecéne. **2:** 308, 1931. *Rokitansky, C.:* Wein. allg. med. Zeitung. **34:** 35, 1859. *Santi, E.:* Monatschr. f. Geburtsh. u. Gynäk. **20:** 76, 1904. *Schaller and Pförringer:* Beitr. Geburtsh. u. Gynäk. **2:** 91, 1899. *Wolfe, S.:* Am. J. Obst. & Gynec. **13:** 575, 1927. *Wills, S. H., and Romano, S. A.:* Ibid. **29:** 845, 1935.

General: Brambell, F. W.: Proc. Roy. Soc. Lon. B. **101:** 391, 1927. *Brambell, F. W., Parkes, A. S., and Fielding:* Proc. Roy. Soc. Lon. B. **101:** 29, 1927. *Dantschakoff, W.:* Ztschr. f. Zellforsch. u. mikr. Anat. **18:** 56, 1933. *Firket, J.:* Anat. Rec. **18:** 309, 1920. *Fischel:* Ztschr. f. Anat. u. Entwcklngsgesch. **92:** 34, 1930. *Parkes, A. S.:* Proc. Roy. Soc. Lon. B. **100:** 172, 1926; **101:** 71 and 421, 1927. *Parkes, A. S., and Brambell, F. W.:* Proc. Roy. Soc. Lon. B. **101:** 328, 1927. *Stieve, H.:* Ztschr. f. mikr. Anat. Forsch. **10:** 225, 1927. *Swingle, W. W.:* J. Exper. Zool. **32:** 235, 1921. *Tietze, K.:* Arch. f. Gynäk. **148:** 724, 1932.

DISCUSSION

DR. SAMUEL H. GEIST.—The histogenesis of granulosa cell tumors of the ovary is still a subject of considerable discussion. Fischel's theory that the ovarian parenchyma is the result of the differentiation of the mesenchymal cell mass is being accepted by a large number of embryologists. Fischel's theory is more logical in that it conforms to the accepted belief of the development of other organs.

The ovum is surrounded by a single row of parenchymal cells, i.e. follicular cells and the further development of the follicle cells is the result of the proliferation of

the original circlet of cells. The vast mass of the ovary which is so frequently called stroma, but which I prefer to call parenchyma, contains not only connective tissue elements but a vast number of differentiated mesenchymal cells which have the potentiality to become either granulosa or theca or possibly other cell types, and I believe that it is from these parenchymal cells that the granulosa and theca cell neoplasms arise. This concept would more readily explain why such tumors develop after the menopause, when the follicles have degenerated and the follicular epithelial growth no longer exists. The parenchyma undoubtedly contains structures capable of further development when properly stimulated. What the stimulus is at the present time is unknown. The slides that Dr. Traut demonstrated of the mouse tumors seem to me to add weight to the concept of the histogenesis of the granulosa and theca cell type of tumors.

It is possible that one may get combination tumors such as the following: The patient was past the menopause and complained of bleeding. Robert Meyer, who saw sections of the growth, thought that the tumor might be an arrhenoblastoma but hormonal study of the tumor tissue showed that it contained a considerable amount of estrin. It is perfectly reasonable to suppose that a tumor can be composed of two components responding to a common stimulus and the result of such a growth might be a tumor presenting characteristics of each type. In the instance above quoted the possibility of an arrhenoblastoma in association with a granulosa cell tumor can be entertained. The symptomatology may at times be confusing. We may have a clinical picture which does not conform to the type we anticipate, such as the masculization associated with the tumor of the granulosa cell type, but it is only a question of time when the clinician and laboratory worker will have sufficient material to enable him to classify these growths.

Dr. Traut suggests that luteoma represents the luteinization of either a granulosa cell tumor or a theca cell tumor, and with that concept I am entirely in accord. I do not believe that the tumor can arise from a completed granulosa lutein cell. The term granulosa lutein cell is applied to a granulosa cell that has undergone a definite lipoid change, and such cells if they were capable of reproduction would reproduce as normal granulosa cells and not as luteinized cells. Yet, I believe that in many instances the tumors that have been reported as luteomas were either metatastic hypernephroma or tumors arising from aberrant adrenal cortical tissue. Furthermore in many instances the symptom associated with luteoma strikingly resembles the symptom complex associated with adrenal cortical neoplasm. One so-called luteoma that I had an occasion to examine and which had been reported in the literature turned out to be a Krukenberg tumor.

DR. HOWARD C. TAYLOR.—Dr. Traut and Dr. Geist have covered the embryologic aspects of this subject exhaustively. I wish, therefore, to make a few clinical points in regard to the frequency of these tumors, and to the symptoms they give rise to.

On the gynecologic service of the Roosevelt Hospital, there were treated 405 cases of bleeding after the menopause during a fifteen-year period. Of those cases, there were only four that belonged to the group under discussion. Hence if you have a case of postmenopausal bleeding, the chances are, roughly, one hundred to one that a granulosa cell tumor is not present. In the 405 cases, there were in all 23 cases of ovarian tumor. Besides the 4 granulosa cell tumors, there were 8 typical adenocarcinomas of the ovary, and 11 miscellaneous benign tumors, most of them pseudomucinous cystadenoma. Hence if you have a case of bleeding after the menopause even when associated with an ovarian mass, the chances are still five to one that you are not dealing with a granulosa cell tumor.

When you have this combination of a palpable ovarian tumor with bleeding in the postmenopausal period, the bleeding may be due to several causes. In the first place, if you have a carcinoma of the ovary, you are liable to have an associated carcinoma of the endometrium. The bleeding is then due to the endometrial and not to the ovarian lesion. In the second place, a certain number of uteri with ovarian tumors bleed, in spite of the fact that the endometrium is atrophic. Various explanations have been given for this. Possibly the presence of a large tumor in the pelvis produces congestion of the blood vessels of the endometrium. There is a suggestion in the literature that some of the nonspecific tumors have some effect finally on the endometrium, such as one or two reports of hyperplastic changes in the endometrium associated with pseudomucinous cystadenoma. (Lantern slide demonstration of 4 tumors of granulosa cell group.)

DR. ONSLOW A. GORDON, JR.—The clinical diagnosis of these tumors is not as a rule difficult when they occur before puberty or after the menopause. When they originate during active sexual life the diagnosis is much more difficult. After the menopause, the first procedure is curettage, and in most of these cases this will reveal a definitely hyperplastic endometrium without evidence of malignancy. With postmenopausal bleeding of a somewhat regular type, not irregular spotting or scant metrorrhagia, associated with a hyperplasia of the endometrium, one is fairly well justified in making a diagnosis of granulosa cell tumor.

In each of two cases of granulosa cell tumor I have recently seen there had been a provisional diagnosis of carcinoma of the corpus, but curettage of each yielded a definite hyperplastic endometrium. One of these patients subsequently came into the Gynecological Service at Long Island College Hospital and has been reported by Drs. Kaminester and Wolfe. That patient had a curettage followed by intrauterine radiation and x-ray, but the bleeding recurred and a granulosa cell tumor was later removed.

The second patient was first seen in 1926 when fifty years of age, suffering from menorrhagia of a regular type. She had not passed through the menopause. The uterus was definitely myomatous, about the size of a three months' gestation. Because of a recent operation for cholecystitis, it was thought unwise to treat her menorrhagia by laparotomy, and so she received x-ray radiation. This controlled her bleeding and produced an absolute amenorrhea of eight years' duration. In 1934, when fifty-nine years of age, she began to have metrorrhagia resembling somewhat menstruation in type and a diagnostic curettage was done. The histologic findings showed simply hyperplasia of the endometrium with no evidence of malignancy. At the time of curettage radium was introduced into the body of the uterus, and she was given 2,400 mg. hr. intrauterine radiation. Bleeding, however, did not cease entirely. A diagnosis of granulosa cell tumor of the ovary was then made, and in 1935 she had a complete hysterectomy with a bilateral salpingo-oophorectomy. The unilateral ovarian tumor measured 6 cm. in diameter and was classified as a granulosa cell tumor growth. This case is very interesting and emphasizes the point made recently by Studdiford that many of these tumors are exceedingly radioresistant.

DR. SAMUEL A. WOLFE.—The need for the study of the criteria of malignancy in this group is shown by the varying reports on the frequency of malignant examples. In Schiller's series of 24 cases, 8, or 33 per cent, were malignant. In Habbe's series of 70 cases, 14 per cent were clinically malignant. In the largest series in this country (Novak and Brauner), there was an incidence of malignancy in 28.1 per cent of the cases. Large numbers of mitotic figures are suggestive. Variation in the size and shape of the nuclei is of special significance only if cells of similar pattern are studied.

Though it is a little early to formulate a final rule of therapy, the following plan is presented. A well-encapsulated, unilateral, granulosa cell tumor in a woman in the childbearing age, requires only simple salpingo-oophorectomy. If the tumor is bilateral, it has clinically, at least, malignant potentialities. Complete hysterectomy and bilateral salpingo-oophorectomy are indicated. In frankly malignant cases, the treatment should be that of any other ovarian malignancy, surgical removal of as much of the tumor and contiguous tissue as possible, followed by deep x-ray therapy. The reports on the efficacy of the latter agent are contradictory in the literature. The records of dosage are so unsatisfactory that no conclusions appear warranted.

DR. SANFORD KAMINESTER.—The possible effects of irradiation on this tumor in human beings has been brought out. The first tumor Dr. Gordon referred to was some 6 cm. in diameter. Although the uterus showed extensive change as a result of the radium treatment, the ovarian growth had not been affected. We were unable to say whether or not the tumor was present at the time radium was first employed.

In another case at the Long Island College Hospital, the patient had postmenopausal bleeding for which she was treated with radium. At the time, she presented no evidence of any tumor. Six months later, however, there was a large mass in the pelvis. When it was removed, the mass was found to be a granulosa cell carcinoma. This patient died within eight weeks of operation.

EXPERIENCE IN THE TREATMENT OF CARCINOMA OF THE FUNDUS OF THE UTERUS, WITH FIVE-YEAR END-RESULTS IN FORTY-SEVEN PATIENTS*

LEWIS C. SCHEFFEY, M.D., AND WILLIAM J. THUDIUM, M.D.,
PHILADELPHIA, PA.

(From the Department of Gynecology and the Tumor Clinic, Jefferson Medical College Hospital)

THE experiences here related concern 68 consecutive patients admitted to the ward and private services of Dr. Brooke M. Anspach and associates, Department of Gynecology, Jefferson Medical College Hospital, from Sept. 1, 1921, to Sept. 1, 1936, in each of whom a diagnosis of carcinoma of the uterine fundus was substantiated histologically. The study provides a basis: first, for a review of certain points of general interest relative to the entire group; second, for a discussion of the treatment and end-results observed in a five-year series totaling 47 patients. There are no untraced patients.

AGE INCIDENCE, PARITY, AND RACE

On admission, 55 patients were between the ages of fifty and seventy (80.9 per cent). Thirteen were under the age of fifty (19.1 per cent). The youngest patient in the series was thirty-seven, the only one in the group under forty years of age; the oldest was sixty-nine. Two patients were Jewish; only one was a negress.

Twenty-five were nulliparous (36.7 per cent), of whom 13 were unmarried.

*Read at a meeting of the Obstetrical Society of Philadelphia, March 4, 1937.

The proportion of patients with fundal carcinoma admitted to the ward service, when compared with those admitted with cervical carcinoma during the same period, was 1:9.58 (Table I).

TABLE I. AGE INCIDENCE, PARITY, RACE

DECADE	PATIENTS	PER CENT
30-39	1	1.5
40-49	12	17.6
50-59	32	47.1
60-69	23	33.8
Total	68	100.0

Youngest, 37; oldest, 69
Nulliparas, 25; 36.7 per cent (13 unmarried)
Negro, 1; 1.5 per cent
Ratio of carcinoma of cervix (ward service) 1:9.58

MENOPAUSAL RELATIONSHIP

Sixteen patients (23.5 per cent), whose average age was 47.1 years, had experienced no cessation of periodic bleeding prior to the onset of symptoms, and for practical purposes are regarded as a premenopausal group. However, 6 of these patients were over fifty years of age, and it is quite possible that what they regarded as regular menstrual periods were in fact intermittent periods of bleeding associated with their malignant disease.

Fifty-two patients (76.5 per cent), whose average age was 58.8 years, had definitely passed the menopause when symptoms began, within one to fifteen years thereafter in 80 per cent of cases. In 3 instances symptoms did not make their appearance until twenty to thirty years after the established menopause (Table II).

TABLE II. MENOPAUSAL RELATIONSHIP

GROUP	PATIENTS	PER CENT	AVERAGE AGE
Premenopausal	16	23.5	47.1 yr.
Postmenopausal	52	76.5	58.8 yr.

SIGNIFICANCE AND DURATION OF SYMPTOMS

Irregular uterine bleeding of some variety was the principal symptom exhibited by 95.6 per cent of all the patients. It varied from slight bleeding or bloody discharge (''spotting'') to frank hemorrhage. In the premenopausal group, metrorrhagia and menorrhagia were equally divided in frequency; among the postmenopausal patients, ''spotting,'' gradually increasing in amount and frequency, was of most significance. In only 3 patients (4.4 per cent) was there no irregular bleeding of any sort, the initial symptom in one patient being a metastatic nodule in the anterior vaginal wall, appearing ten years after the menopause. Among those patients in whom menstruation had not yet ceased, the duration of symptoms prior to treatment averaged 9.5 months; in the postmenopausal group it was 15.2 months. Approximately one-third of the patients (33.8 per cent) sought advice from one to six months after the irregularity began.

The significance of vaginal discharge and its diagnostic importance is difficult to evaluate.

Nearly half of the patients (47 per cent) emphasized the occurrence of discharge, over periods of months or years, but its diagnostic import was of minor character when compared with the predominant symptom of unusual bleeding.

Pain was likewise complained of by about half of the patients (47 per cent); it was not identical with the group complaining of discharge. With the exception of those patients presenting advanced lesions, responsibility might well be assigned to other causes: associated pelvic lesions, intestinal disturbances, extrinsic factors (i.e. bladder irritability, osteoarthritic manifestations) or to the infirmities of advancing years: diverse annoyances, simply interpreted by the patient as "pain." It is not rational to believe that localized malignancy of the fundus, per se, even though progressive, can initiate pain of diagnostic significance (Table III).

TABLE III. SIGNIFICANCE AND DURATION OF SYMPTOMS

GROUP	PATIENTS	IRREGULAR BLEEDING	AVERAGE DURATION	DISCHARGE	PAIN
Premenstrual	16	14	9.5 mo.	8	6
Postmenopausal	52	51	15.2 mo.	24	26
Total	68	65		32	32
Per cent	100	95.6		47	47

Metrorrhagia and menorrhagia occurring in the premenopausal epoch, and postmenopausal "spotting" or frank bleeding are of primary importance in directing attention to the necessity of excluding carcinoma; leucorrheal discharge and pain are of lesser importance except so far as their presence may influence the patient to seek medical advice.

DIAGNOSIS

The diagnosis was correctly suspected from the symptomatology in 60 patients (88.2 per cent), being confirmed in 54 by diagnostic curettage; in the remaining 6 patients operative treatment was immediately resorted to without curettage, on the basis of the clinical diagnosis and correctly so, as proved by pathologic examination of the removed uteri.

In 19 patients suspected of having carcinoma diagnostic curettage was a preliminary step prior to instituting treatment; in 35 patients, it was carried out at the time of treatment, confirming the strong suspicion of cancer. (In 4 patients, preliminary curettage had been done elsewhere, the procedure being rechecked in three instances when initial radiation treatment was given, while in one, immediate surgical treatment was favored on the basis of the pathologic slide submitted.)

In 8 patients (11.8 per cent) not suspected of having carcinoma, the value of diagnostic curettage is well illustrated, for in 3 of them the procedure revealed the lesion, and proper treatment was planned accordingly. In 4 patients in whom carcinoma was not suspected, the omission of diagnostic curettage was costly, resulting primarily in incomplete plans of treatment which might otherwise have been avoided. Finally, in one patient, although preliminary curettage was performed routinely, the curettings did not excite suspicion, and it was only when an incision was made that the presence of bilateral ovarian carcinoma, secondary to a fundal lesion, revealed the true state of affairs (Table IV).

TABLE IV. DIAGNOSIS

DIAGNOSIS	PATIENTS	PER CENT	PRELIMINARY DILATATION AND CURETTAGE	NO DILATATION AND CURETTAGE
Suspected	60	88.2	54	6
Unsuspected	8	11.8	4	4

These observations confirm and emphasize the well-recognized value of diagnostic curettage, performed circumspectly, and with due regard for the potential dangers accompanying its use, to which Sampson[1] has so forcefully called our attention.

ASSOCIATED PATHOLOGY

The well-recognized association between uterine fibroids and carcinoma of the endometrium was borne out in this series, being noted in 16 patients (23.5 per cent). On two occasions, in patients in the premenopausal group, fibromyoma was the dominant lesion and treatment was based on this assumption; accompanying carcinoma was not suspected and not recognized until the abdominal cavity was exposed. As noted previously, these were two of the four instances in which preliminary curettage would have avoided an incorrect diagnosis.

Extension of carcinoma to the ovaries, tubes, peritoneum, omentum, or intestine was noted in 9 patients (13.2 per cent). Enlarged pelvic glands, induration of the broad ligaments, adnexal and sigmoidal adhesions were likewise noted one or more times among 9 patients (13.2 per cent). Carcinoma elsewhere, independent of the fundal malignancy, was present in five patients: breast, 3; stomach, 1; sigmoid, 1. Benign ovarian tumors were found three times, benign cervical polyps twice.

Three patients had prolapse of the uterus of varying degree; 2 amounted to complete procidentia, and this association with carcinoma has been reported in a previous communication.[2]

The association with diabetes is rather surprising. It was an accompanying condition in 7 patients (10.2 per cent). Varying degrees of obesity, cardiorenal and cardiovascular disease were encountered. Three suffered from gallbladder disease; one patient each had chronic pulmonary tuberculosis, chronic phlebitis and hemiplegia, respectively.

It is interesting to note that in 52 patients (77.6 per cent) the hemoglobin estimation on admission was 70 per cent or higher, while 54 patients (81.8 per cent) had red blood cell counts of 3,500,000 or higher. The leucocyte count was under 9,000 in 37 patients (56 per cent); above 9,000 in 29 patients (44 per cent). The lowest count noted was 4,100; the highest 21,300. In view of the comparatively long duration of symptoms presented by most patients prior to treatment, these readings seem peculiarly high in the case of the hemoglobin and red blood cell estimations; the leucocyte counts seem more in keeping with the pathology encountered (Table V).

TABLE V. ASSOCIATED PATHOLOGY

LESION	PATIENTS	PER CENT
Fibromyoma uteri	16	23.5
Carcinomatous extension	9	13.2
Induration and adhesions	9	13.2
Diabetes	7	10.2
Concomitant carcinoma	5	7.3
Benign ovarian cyst	3	4.4
Procidentia	2	2.9
Blood Counts:		
Hemoglobin above 70 per cent	52	77.6
R. B. C. above 3½ million	54	81.8
W. B. C. under 9,000	37	56.0
W. B. C. above 9,000	29	44.0

CLINICAL CLASSIFICATION AND HISTOLOGIC GRADING

We have attempted to classify the degree of involvement according to the grouping suggested by the American College of Surgeons. Upon this basis, 50

patients (73.5 per cent) were in Class 1 A (primary case, disease limited to uterine cavity). Sixteen patients (23.5 per cent) were in Class 1 B (primary case, disease involving broad ligaments [ovary]). The remaining 2 were, respectively, in Class 1 C (primary case, vaginal metastasis) and Class 6 A (recurrence after radiation therapy). This patient was treated elsewhere primarily.

Furthermore, in conjunction with and under the direction of Dr. Baxter L. Crawford, Pathologist and Director of Clinical Laboratories at the Jefferson Hospital, all pathologic material was reviewed in order to estimate the degree of malignancy exhibited in each case. With one exception, in which instance the histologic slide and paraffin block could not be found, every specimen was available for review and study.

In the study of our fundal carcinomas we have divided them into three groups as recommended by various authors: Ewing, Mahle, Healy and Cutler. The low grade (corresponding to papillary adenoma malignum and adenoma malignum, Grades I and II); the intermediate group (corresponding to adenocarcinoma, Grade III); the high grade or extremely anaplastic variety (cellular-anaplastic-adenocarcinoma, Grade IV).

This plan of differentiation placed 22 of the carcinomas in the low grade, 27 in the intermediate, and 18 in the high grade histologic grouping, with one unclassified, for the reason previously stated (Table VI). The question of the relationship of endometrial hyperplasia to fundal carcinoma, and a discussion of the so-called "carcinoid" type of lesion has not been included in this presentation.

TYPE OF TREATMENT

In all, 67 of the 68 patients seen have had treatment. From 1921 to 1931, 46 of 47 patients seen were treated and form the basis for an analysis of five-year end-results. Of 46 cases, 13 (28.2 per cent) were subjected to surgery alone; 18 (39.1 per cent) by radiation (radium alone, or in conjunction with x-ray); 15 (32.6 per cent) by surgery in combination with radiation (preliminary radium, and/or with x-ray, or postoperative x-ray). It is significant that since 1931 no

TABLE VI. CLINICAL CLASSIFICATION AND HISTOLOGIC GRADING

GROUPING AMERICAN COLLEGE SURGEONS	PATIENTS	PER CENT
Class 1 A	50	73.5
Class 1 B	16	23.5
Class 1 C	1	1.5
Class 6 A	1	1.5
Histologic Grading		
Low	22	32.3
Intermediate	27	39.7
High	18	26.4
Unclassified	1	1.6

TABLE VII. TYPE OF TREATMENT

YEARS	PATIENTS SEEN	PATIENTS TREATED	SURGERY	RADIATION	SURGERY AND RADIATION
1921-31	47	46	13	18	15
Per cent			28.3	39.1	32.6
1931-36	21	21	6	15	6
Per cent			—	71.4	28.5

case has been treated by surgery alone; that in 15 patients (71.4 per cent) radiation has been used exclusively, surgery in combination with radiation being the treatment of choice in 6 patients (28.5 per cent) (Table VII).

ANALYSIS OF FIVE-YEAR END-RESULTS

As stated in a previous contribution,[3] we re-emphasize our belief that an eight-year limit of freedom from the signs and symptoms of carcinoma is a more desirable criterion of survival than the generally accepted five-year limit, and again suggest that the latter term be qualified by the expression "five-year salvage." We have chosen to evaluate our five-year end-results from two viewpoints:

1. *The General Five-Year Salvage Observed in 47 Patients Seen From 1921 to 1931, Irrespective of the Type of Treatment and Grade of Malignancy.*—Of 47 patients seen, 46 were treated. Twelve are alive and present no demonstrable evidence of recurrent carcinoma, the salvage periods ranging from five to thirteen years, the present ages of the patients varying from fifty-four to seventy-seven years. The present-day salvage therefore is 25.5 per cent absolute and 26 per cent relative. Three additional patients survived from five to eight years, but clinically did not die of carcinoma, increasing the five-year survival period to 31.9 per cent absolute and 32.6 per cent relative. Three patients, who survived from six to seven years after treatment but died of carcinoma, increase the five-year salvage figure to 38 per cent absolute and 39.1 per cent relative, but this is solely of theoretic interest. Twenty-nine patients died of cancer within five years of treatment, most of them within a year, including the untreated case. There were 2 postoperative deaths, a primary mortality for the entire series of 4.3 per cent, or for the patients subjected to hysterectomy, 8.6 per cent (Table VIII).

TABLE VIII. FIVE-YEAR SALVAGE IRRESPECTIVE OF THE TYPE OF TREATMENT AND GRADE OF MALIGNANCY

YEARS	PATIENTS SEEN	PATIENTS TREATED	PRESENT-DAY SALVAGE	5-YEAR SURVIVAL NONCANCER DEATHS	5-YEAR SURVIVAL CANCER DEATHS	PRIMARY MORTALITY
1921-31	47	46	12	3	3	2
Per Cent (Absolute)			25.5	31.9	38.0	4.3 (All cases)
Per Cent (Relative)			26.0	32.6	39.1	8.6 (Hysterectomy)
No untraced patients						

2. *Five-Year Salvage in Relation to the Type of Treatment and Histologic Grouping of the Malignancy.*—A. *Low-Grade Group—15 Patients:* Five patients were treated by *surgery alone,* of whom two have survived the five-year period (40 per cent). They are living six and nine years, respectively, since operation, which was complete abdominal hysterectomy with bilateral salpingo-oophorectomy.

One patient succumbed of general carcinomatosis two months after the complete operation. In another, supravaginal hysterectomy with bilateral salpingo-oophorectomy was performed because technical difficulties (adherent sigmoid) prevented the performance of the planned complete operation. The amputation seemed to be well below the malignant area, and the cervical stump was cauterized from above. Nevertheless the patient died four and one-half years later of metastatic carcinomatosis. Postoperative radiation might have been desirable.

A death, occurring in a woman sixty years old, followed complete abdominal hysterectomy with bilateral salpingo-oophorectomy. On the twelfth postoperative day coma developed and a blood sugar reading of 506 mg. per c.c. was obtained. Although urinalysis prior to operation had been negative, a review of the records showed one positive postoperative specimen, which would indicate that diabetes had probably been overlooked, although at the time her death was attributed to myocardial failure. This fatality might have been prevented had more significance been attached to the postoperative urinalysis.

Five patients were treated by *radiation alone* of whom 2 have survived the five-year period (40 per cent). They are alive and symptom free from six to seven years. One received a single intrauterine application of 5,400 mg. hr.; the other 2,400 mg. hr. followed by one course of x-ray. Three patients died of carcinomatosis within two years. In one of these patients, carcinoma was subsequent to an interposition operation performed two years before. She received 3 intrauterine applications of radium, 300, 3,600, and 2,400 mg. hr., respectively, the small primary dosage at the time of preliminary curettage. The second patient received 2 applications each of 2,400 mg. hr., the third patient receiving 2,400 mg. hr., followed by two courses of x-ray.

Five patients were treated by *surgery in combination with radiation,* of whom 3 survived the five-year period (60 per cent). Two are living and well, seven and eight years, respectively. One remained well of carcinoma but committed suicide eight years after treatment, having developed manic-depressive insanity. Routine curettage in this patient at the time of a plastic and ventral fixation operation, revealed carcinoma. Three thousand six hundred mg. hr. of radium were applied to the uterine cavity followed in eight weeks by complete abdominal hysterectomy with bilateral salpingo-oophorectomy. Necrosis of the uterine cavity, but no evidence of carcinoma was found in any of the removed organs. In the case of the 2 surviving patients, supravaginal hysterectomy with bilateral salpingo-oophorectomy was employed because of technical difficulties encountered (in one, induration of the broad ligaments; in the other, poor reaction to anesthesia), although the diagnosis had been established by preliminary curettage and complete operation planned. In both instances the supravaginal amputation was well below the carcinomatous area and the cervical stump was cauterized from above prior to peritonization. Postoperative x-ray followed in each instance.

Two patients survived from six to seven years but died of carcinoma. In one, the possibility of carcinoma was not recognized grossly in the preliminary curettage, and abdominal section was immediately proceeded with because of the presence of an abdominal tumor. Bilateral ovarian carcinoma was found and removed, and supravaginal hysterectomy was performed. Routine histologic examination revealed fundal carcinoma as well, and 3,000 mg. hr. of radium were subsequently applied to the cervical stump. This patient was lost sight of, only to return seven years later with uremia and generalized abdominal carcinomatosis, proved at autopsy. Postoperative x-ray therapy might possibly have prevented this outcome. In the second patient, preliminary radium and x-ray was followed by complete abdominal hysterectomy with bilateral salpingo-oophorectomy. There was no evidence of carcinoma in the removed organs, but death was eventually due to carcinomatosis.

B. *Intermediate Grade Group—19 Patients:* Five patients were treated by *surgery alone.* Only one survived the five-year period (20 per cent); this patient, treated by complete abdominal hysterectomy with bilateral salpingo-oophorectomy, succumbed of intercurrent disease. A vaginal hysterectomy in a patient with moderate descensus uteri, performed without preliminary curettage, resulted in the removal of a carcinomatous uterus, but not of the adnexa, and the patient died within one year of carcinomatosis. The omission of postoperative radiation is re-

grettable, while preliminary curettage might have resulted in complete operation or a different plan of treatment. Two patients having complete abdominal hysterectomy with bilateral salpingo-oophorectomy succumbed within one year from carcinomatosis.

There was one postoperative death in this group. The patient was forty-seven years old, and the preoperative diagnosis was fibromyoma uteri. Without preliminary curettage, supravaginal hysteromyomectomy with bilateral salpingo-oophorectomy was performed. When fundal carcinoma was discovered in the amputated uterus, the cervical stump was immediately cauterized from above and removed, but death from peritonitis occurred on the seventh postoperative day. Preliminary curettage would probably have indicated a different plan of treatment.

Eight patients were treated by *radiation alone.* Three have survived the five-year period, five, eight, and thirteen years, respectively. One received a single radium treatment (3,600 mg. hr.), while one at the time of diagnostic curettage, received 200 mg. hr., pending the report on the curettings, after which a second application (3,600 mg. hr.) was made. The third received 2,400 mg. hr. of radium followed by one course of x-ray. Two patients, each receiving single applications of 2,400 mg. hr., died within three years; 2 patients, one receiving 4,800 mg. hr. and one course of x-ray, and the other 3,000 mg. hr. and two courses of x-ray, followed by more intrauterine radium (900 mg. hr.) and 600 mg. hr. for vaginal metastases, died within one year. One patient, with concomitant carcinoma of the breast, received one course of deep x-ray therapy only, surviving three and one-half years.

Five patients were treated by *surgery combined with radiation,* of whom one has survived eleven years (20 per cent). The procedure was complete abdominal hysterectomy with bilateral salpingo-oophorectomy followed by x-ray. Two patients, having the complete operation followed by x-ray, died of carcinomatosis within one and four years of operation, respectively. A third patient received intrauterine radium and x-ray prior to operation, which revealed abdominal carcinomatosis with extension to the right tube and ovary which latter organs only were removed. Further x-ray was employed postoperatively. Strangely enough, she survived six years, before dying of carcinoma. In the case of one patient, in whom preliminary curettage was omitted, supravaginal operation for fibromyoma revealed not only carcinoma of the endometrium following the uterine amputation and bilateral salpingo-oophorectomy, but an infiltrating growth in the right broad ligament as well. Radium was applied to this area and postoperative x-ray employed. Three months later the patient died of lobar pneumonia and autopsy demonstrated the persistence of carcinoma in the pelvis.

One untreated patient died of carcinomatosis within four months.

C. *High Grade Group—12 Patients:* Two patients were subjected to *surgery alone* with no survivals. One had received intrauterine radium elsewhere three years before. The reason and dosage could not be ascertained. Complete abdominal hysterectomy with bilateral salpingo-oophorectomy was followed by death from spinal metastasis within a year. The second patient had been subjected elsewhere to 2 intrauterine applications of radium during a period of four years prior to admission, but no histologic study of the curettings had been made and the diagnosis could not be secured. Following a positive curettage, abdominal section revealed carcinomatosis involving the tubes, ovaries, intestines, and omentum. One tube and ovary only could be removed, and the patient died shortly thereafter.

Five patients were treated by *radiation alone,* of whom 2 have survived the five-year period (40 per cent). One is living and well, eight years after treatment (2,400 mg. hr.). The second patient received 3 applications of 2,400, 3,600, and 4,800 mg. hr., respectively, with 2 intervening courses of x-ray. She survived eight years, dying of cardiorenal disease complicating chronic pulmonary tuberculosis from which she suffered when first seen. The remaining 3 patients died within

three and one-half years of treatment. One had received a single treatment (2,200 mg. hr.); a second, two treatments (2,400 and 1,200 mg. hr., respectively); the third a single treatment (7,200 mg. hr.) followed by further radiation elsewhere.

Five patients received *surgical treatment with radiation* in addition. None have survived the five-year period. One patient (aged forty-three) had been treated elsewhere with radium seven years before for functional bleeding. Following complete operation (without curettage), vaginal metastasis and death occurred within a year, with intervening postoperative radiation. A second patient (aged forty-two) had also received radium elsewhere nine years before for functional bleeding. Following preliminary intrauterine radiation (2,400 mg. hr.) complete abdominal hysterectomy, with right salpingo-oophorectomy was performed. The left adnexa, adherent to the sigmoid, was of necessity allowed to remain in situ. The endometrial cavity was necrotic but invasion of the uterine wall was present. Two courses of postoperative x-ray were employed, death from carcinomatosis occurring within three years. A third patient (aged forty-five) received 2,400 mg. hr. of radium preoperatively, followed by complete operation. Although the endometrium was necrotic and there was no evidence of carcinoma in the uterus, metastasis in one ovary was found. Postoperative x-ray was followed by death from metastatic carcinomatosis within a year. Operation was abandoned in 2 patients after the abdomen was opened, radium (3 applications: 5,100 mg. hr., 1,200 mg. hr., 2,400 mg. hr., respectively) and x-ray being employed in one, and x-ray only in the other.

The patient whose histologic slide was not available for classification has survived treatment twelve years and is quite well. It is unfortunate that both the block and slide are missing, for it would be desirable to know the specific characteristics of the adenocarcinoma in this instance. We hope that continued search will be successful for use in subsequent reports (Table IX).

TABLE IX. FIVE-YEAR SALVAGE IN RELATION TO THE TYPE OF TREATMENT AND HISTOLOGIC GROUPING OF MALIGNANCY

GRADE OF MALIGNANCY	SURGERY	RADIATION	SURGERY AND RADIATION	5-YEAR SALVAGE GRADE OF MALIGNANCY
Low	2 of 5 40%	2 of 5 40%	3 of 5 60%	7 of 15 46.6%
Intermediate	1 of 5 20%	3 of 8 37.5%	1 of 5 20%	5 of 18 27.7%
High	0 of 2 —	2 of 5 40%	0 of 5 —	2 of 12 16.6%
Five-year salvage, type of treatment	25%	39%	20.6%	

(One surgical patient surviving twelve years has been unclassified histologically)

DISCUSSION

The radium employed was screened with 0.3 mm. of silver, 1.0 mm. of brass, and protected with 2.0 mm. of black rubber tubing. The x-ray therapy has been and is carried out in the Department of Roentgenology at Jefferson Hospital with the cooperation of and under the direct supervision of the late Dr. Willis F. Manges, and his associates Drs. John T. Farrell, Jr., and Manges Smith. The technic has been described in detail in a recent contribution.[3] Since August, 1927, the factors used in the treatment are 200 kilovolts, 50 cm. distance filtered

through 0.5 mm. of copper and 1.0 mm. of aluminum. The output on the machine is 18.5 r. per minute when 8 ma. are used and the erythema dose is estimated at 800 r. The dosage delivered through each port by this method varies from 1400 to 2500 r.

During the earlier years covered by this report, complete operation was thought to be the treatment of choice for carcinoma of the fundus. Patients obviously not suited for surgery were treated with radium and x-ray. In 1926 we began definitely to combine surgical treatment with radiation therapy. Radium was then used as a preliminary procedure, and complete hysterectomy was sometimes followed by x-ray postoperatively. A plan of treatment evolved at that time and continued with some modification is at present as follows: When a patient is seen in whom carcinoma of the fundus is suspected, diagnostic curettage is carried out and 50 or 100 mg. of radium are available for intrauterine application. If a frozen section of the curettings establishes the diagnosis of malignancy beyond question, the radium is allowed to remain in situ for a designated time. Subsequent treatment, whether by further radiation or by combined radiation and surgery, is dependent upon the clinical picture and the grade of malignancy as determined by a thorough study of rapidly prepared (24 hr.) paraffin sections. If an accurate diagnosis cannot be made from the frozen section the radium, usually 50 mg. in this instance, is not removed until the exact diagnosis has been determined from the rapid paraffin section. If carcinoma is not present, the radium therapy that has been employed is usually adequate to control the symptoms.

Furthermore, we have come to the conclusion that if carcinoma has been diagnosed, is clinically limited to the uterus, and the patient is a reasonably good operative risk, that complete abdominal hysterectomy with adnexal extirpation from six to ten weeks after radiation is the preferable procedure, especially if we are dealing with a low grade type of malignancy. Operation by the vaginal route may sometimes be a better plan. The question of giving preliminary x-ray therapy during this time in addition to the radium already applied depends upon the physical characteristics of the patient. It is generally agreed that the obese patient with a thick pendulous abdomen and heavy buttocks, or the extremely thin devitalized individual, is not a good subject for external radiation. It may be wiser in these circumstances to depend upon radium alone for preliminary radiation.

When an intermediate or high grade type of malignancy is present, when the disease has markedly advanced clinically, or when the patient's general condition makes operation definitely hazardous, our experience has shown that radiation may well be regarded as the treatment of choice. It should be stated, however, that individual circumstances may indicate subsequent operation, even though the lesion is of an intermediate or high grade type.

Subsequent test curettage may give a false sense of security, but it is our belief that if after adequate radiation, either with radium alone or combined with x-ray, no bleeding recurs, and none can be provoked by probing the uterine cavity with a sterile sound, the prognosis may be regarded favorably.

From 1931 to 1936 twenty-one additional patients have been seen and treated. Of these 13 are alive for periods varying from one to nearly five years after treatment. Nine are symptom-free, while 4 either show evidence of recurrence or are still under treatment. Eight patients have died within one to three years of treatment. While a detailed analysis of this group would be of interest, time and space do not permit of its inclusion in this presentation.

Observations from this series may be summarized as follows:

1. Four out of 5 women with carcinoma of the fundus developed it after the age of fifty; in 3 out of 4 it was postmenopausal in onset.

2. Irregular uterine bleeding was the predominant symptom. Discharge and pain were of minor diagnostic significance.

3. The advantage of diagnostic curettage outweighs its potentiality for harm. This is especially true of those patients who may develop carcinoma prior to the menopause when more obvious pathology, notably fibromyoma uteri, may appear to be the predominant lesion.

4. Carcinoma of the fundus should be graded as to its degree of malignancy, but as simply as possible. While the folly of attempting to base a prognosis entirely on the gradation of the cell type of growth is obvious, it is plausible to believe that careful consideration of the stage of differentiation of the tumor cells, together with the clinical features of the case, is of distinct value in planning treatment and evaluating the chance of survival.

5. The trend of the results obtained, as presented in this series, is in general accord with the observations of Healy.[4] The best results, regardless of the type of treatment, were obtained in the low grade malignancy group. Radiation alone gave the best end-results when all groups were considered, and was particularly efficacious in the intermediate and high grade groups. When surgery was employed the results were better when it was combined with radiation. Newell and Crossen,[5] however, have wisely pointed out the error which may result from the evaluation of results obtained with one form of treatment when compared with that applied to patients exhibiting different clinical stages of the disease.

6. The ultimate prognosis depends upon factors other than the grade of malignancy. Primarily they are clinical and relate to the age and physical condition of the patient, the duration of symptoms, the promptitude of diagnosis, and the extent of the disease. Secondarily they relate to treatment. Surgery alone has definite limitations; it should prove more efficacious when combined with radiation.

While radium therapy in carcinoma of the fundus, either alone or in combination with x-ray, offers much and has proved its worth, the carefully considered objections that have been voiced by Sampson[1] are based on rational grounds, and the evidence presented is illustrative not only of the contraindications that may be encountered, but is probably explanatory of certain therapeutic failures. These objections may possibly be overcome in part at least, by more effective intrauterine radiation. Burnam,[6] Bowing and Fricke,[7] and Schmitz[8] in this country, and more recently Heyman[9] at Radiumhemmet have devised improved techniques that may aid materially in solving this phase of the problem. Continued improvement in the application of x-ray therapy likewise enters into the solution; theoretically ideal, it cannot always be employed to full advantage because of physical contraindications and intolerance to its effect.

7. Each patient with carcinoma of the fundus presents an individual problem in treatment, the management of which depends upon a thoughtful evaluation of all the factors concerned, and for which no "standardized" plan of therapy can be offered.

REFERENCES

(1) *Sampson, J. A.:* Am. J. Obst. & Gynec. **28**: 783, 1934. (2) *Scheffey, L. C.,* Ibid. **28**: 214, 1934. (3) *Scheffey, L. C., and Thudium, W. J.:* Ibid. **31**: 946, 1936. (4) *Healy, W. P.:* Ibid. **27**: 1, 1934; Am. J. Surg. **33**: 474, 1936. (5) *Newell, Q. U., and Crossen, H. S.:* Am. J. Obst. & Gynec. **29**: 326, 1935. (6) *Burnam, C. F.:* Curtis, Obstetrics and Gynecology **3**: 915, 1933. (7) *Bowing, H. H., and Fricke, R. E.:* Am. J. Roentgenol. **33**: 1, 1935. (8) *Schmitz, H., and Schmitz, H. E.:* Ibid. **34**: 759, 1935. (9) *Heyman, J.:* Acta Radiologica, 16, Fasc. **2**: 129, 1935.

Medical Tower, 255 South 17th Street
Medical Arts Building, 16th and Walnut Streets

DISCUSSION

DR. F. SIDNEY DUNNE.—During the past year, in collaboration with Charles C. Norris, I reviewed the results of 211 cases of carcinoma of the fundus treated at the Hospital of the University of Pennsylvania. This series corresponded very closely with Dr. Scheffey's cases as regards age and symptoms.

With regard to the results of our treatment, the salvage was approximately the same in the group treated by hysterectomy as by irradiation, namely, 47.8 per cent and 43.8 per cent, respectively. It must be pointed out, however, that only 72.1 per cent of the hysterectomy patients were traced as compared with 92.1 per cent of the irradiated cases. Furthermore, in the group treated by hysterectomy the complete operation (panhysterectomy) yielded a salvage of 53.7 per cent compared with 34.3 per cent in the incomplete operation.

It is agreed that in the inoperable case, or in the patients in whom operation is technically difficult or contraindicated, irradiation alone is the treatment of choice. In the operable group, for those skilled in gynecologic surgery, operation offers the best chance for cure. However, statistics from some clinics tend to show that irradiation alone may give at least as good results as operation and is to be considered the method of choice if the patient is to be treated by one not skilled in gynecologic surgery. Healey, at the Memorial Hospital, advocates preliminary irradiation preceding panhysterectomy in the operable cases. The question of preliminary and postoperative irradiation is still controversial.

A personal factor enters into all grading of carcinoma, and it must be remembered that more than one area of carcinoma should be studied, as the same tumor may show different grades in different areas. Thus, while the histologic type is an aid in forming a decision as to the method of treatment, other factors, as extent of the disease, technical operability, contraindication to surgery, etc., have to be considered.

DR. CHARLES A. BEHNEY.—Dr. Scheffey's observation that the danger of curettage is more than compensated for by the advantage of the information gained thereby, is in agreement with the opinions of most of us. I should like to call attention to a more dangerous procedure which has been recommended as a diagnostic aid; namely, the introduction of opaque substance under pressure into the uterus, suspected of being affected by carcinoma. At the Hospital of the University of Pennsylvania, there have been two cases of fundal carcinoma where after curettage, radium was inserted through a small cervical canal. After operation, in one instance, malignant curettings were discovered in a fallopian tube and in the culdesac in the second. Evidently the fragments had been "pumped" into the tubes by the piston-like action of the radium capsule. Before inserting radium into the uterus, one should be certain that the canal is well dilated beyond the dimensions of the tube.

The high percentage of patients in Scheffey's series with postmenopausal carcinoma and the relatively long period of bleeding before their seeking treatment as compared with the patients with premenopausal bleeding, again illustrates the fallacious impression of laymen and some physicians, that irregular bleeding at the time of the menopause can be temporized with.

While complete hysterectomy is the operation indicated for this disease, it must be remembered that in the most difficult cases complete removal cannot always be done with safety. These offer the worst prognosis and when included in any series may exaggerate the disadvantage of the supravaginal operation. Our experience at the Philadelphia General Hospital Tumor Clinic indicates that routine preliminary x-ray irradiation will render a greater proportion of our patients suitable for total hysterectomy than if this preparatory irradiation is omitted.

BROOKE M. ANSPACH.—At one time I thought the treatment of carcinoma of the fundus was a very simple matter. If a diagnostic curettage revealed a carcinoma of the fundus, a complete hysterectomy was to be performed forthwith. It was my impression that at least 75 per cent of the patients were cured. However, when statistics are analyzed, one finds how mistaken that idea is and what a low percentage there is of permanent recovery.

Diagnostic curettage is not always satisfactory to give a complete diagnosis. In Heymann's report of his treatment of cancer with radium, he points out that sometimes pathologists of equal distinction disagree in separating the benign from the malignant. Furthermore diagnostic curettage may not be done without some risk. In two patients coming under my observation, diagnostic curettage was followed by the development of carcinoma of the tibia, evidently metastatic. In the first I did a complete hysterectomy a few days after curettage and found that the carcinoma had advanced into the uterine wall almost to the serosa. The postoperative recovery was uneventful until the last hospital day when the patient complained of pain and tenderness in the shin.

In a second case during the last year, radium had been used elsewhere in small dose without diagnostic curettage. The symptoms continued. We did a gentle curettage and applied radium in full dose. The patient died three months later with carcinoma of the tibia.

Sometimes it might prove better in a case in which the condition bears all the earmarks of a carcinoma to do a hysterectomy without a preliminary curettage, but, of course, we must face the fact that we may remove the uterus needlessly in poor operative risks.

DR. SCHEFFEY (closing).—Several of these patients were treated by supravaginal hysterectomy either by oversight or necessity. Two of the survivors, exhibiting low-grade malignancies, were treated in this manner. The complete operation had been planned, but extensive induration of the broad ligaments made it impossible to do so in one instance. These patients received x-ray postoperatively and remain in the salvaged group.

I do not wish to give the impression that prognosis depends on the cell type alone. It is merely one factor. I agree that such varied pathology may appear in one slide, that a single piece of tissue may not be sufficient to establish gradation, and that several should be examined.

In this series we have shown clearly that the advantages of the curette far outweigh the objections which have been raised by some. Each case is an individual problem and the treatment, therefore, must be based on the consideration of all factors concerned.

THE NITROGEN BALANCE OF A YOUNG PRIMIPARA*

WALTER H. SEEGERS, PH.D., YELLOW SPRINGS, OHIO

(From the Samuel S. Fels Research Institute, Antioch College)

THE protein requirements during pregnancy are probably more clearly defined, on the basis of data available, than those of any other dietary constituent; it is possible to study the metabolism of any one individual and compare the result with an abundance of figures in the literature. Since little is known about the metabolism of comparatively young individuals during pregnancy, it seemed desirable to study such a case when it was available. The primipara whose nitrogen balance was studied during the last trimester of pregnancy was fifteen years and twenty-five days old when she was delivered of a healthy female child weighing 7 pounds.

The metabolism periods were three days in length, and, although the first two days were considered preliminary, the urine was analyzed each day. The feces was marked with carbon and carmine, and Kjeldahl analyses were made on wet samples. She ate one diet (diet A) for seven three-day periods at two-week intervals. Two other diets were also eaten on three-day metabolism periods, and in addition daily food and urinalyses were made for twenty-one consecutive days (see Fig. 1 for distribution of metabolism periods), during which time the diet was variable and self-chosen. Fecal analyses for this last mentioned period were done on pooled excretions.

The subject lived at Fels House and was constantly under observation when dietary studies were in progress. Her food was prepared and carefully weighed for her and a quantity representing half the amount she ate was dried at low temperatures, ground fine in a mortar and analyzed. Diet A was repeatedly analyzed for the purpose of learning how well the nitrogen content of a mixed human diet can be reproduced. Though this matter of diet constancy is of importance in judging the validity of conclusions in any experiment in which a given diet must be repro-

*Published with the permission of the director of the research institute, Dr. L. W. Sontag.

duced, data indicating how well this can be done are not available. The results of our analyses were as follows:

DATE OF SAMPLING	NITROGEN CONTENT IN GRAMS
4/24/36	13.216
5/ 7/36	13.500
5/21/36	13.622
6/ 3/36	13.875
6/ 4/36	13.501
6/18/36	13.328
7/ 2/36	13.573
Average	13.516 ± 0.05
Coef. of Var.	1.4

This diet was, so far as could be judged from our present knowledge of dietetics, adequate in all respects. Principal sources of protein were milk, fish, pork, cereal, and peas. The subject's appetite was good and she never failed to eat the whole meal, but found the diet rather "filling" as pregnancy progressed.

The figures for the nitrogen utilization of the young woman whose study is the subject of this paper were compared with the averages, by months, of a large number

TABLE I. NITROGEN BALANCES DURING PREGNANCY

DAYS BEFORE DELIVERY	BODY WEIGHT KG.	FOOD NITROGEN GM.	URINE NITROGEN GM.	FECES NITROGEN GM.	NITROGEN BALANCE	APPARENT DIGESTIBILITY PER CENT
115	46.4	9.75	8.69	1.23	−0.17	88.4
101	49.5	13.52	9.12	1.52	1.93*	81.7†
88	51.8	13.52	9.21	2.61	1.84*	
86 to 72	51.9	11.82	8.76	1.75	1.31	88.9
71 to 61	52.3	11.70	8.70	1.44	1.56	86.6
60	53.6	13.52	9.24	2.67	1.81*	
46	54.5	13.52	9.05	‡	2.00*	
32	56.8	13.52	7.54	3.33	3.51*	
18	57.7	13.52	6.91	2.22	4.14*	
5	56.9	8.47	6.38	1.65	0.44	80.5

*Computed by using the average digestibility of diet A.

†Average apparent digestibility for diet A.

‡It was not possible to obtain a feces sample because her physician had prescribed colloidal iron as a therapeutic measure. This also made it impossible to make other desirable fecal demarcations.

TABLE II. COMPARATIVE NITROGEN INTAKE AND RETENTION PER KILOGRAM BODY WEIGHT

DAYS BEFORE DELIVERY		FOOD NITROGEN INTAKE GM.		NITROGEN BALANCE GM.	
115	126-102*	0.210	0.255*	−0.004	0.040*
101	101- 77	0.273	0.248	0.039	0.037
88		0.261		0.036	
86-72		0.228		0.025	
71-61	76- 52	0.224	0.266	0.030	0.054
60		0.252		0.034	
46	51- 27	0.248	0.243	0.037	0.030
32		0.238		0.062	
18	26- 1	0.234	0.237	0.072	0.040
5		0.149		0.008	
	Average	0.232	0.250	0.034	0.040

*Data in these columns arranged from the continuous metabolism study of Hummel, Sternberger, Hunscher and Macy.[1]

of subjects previously studied in various laboratories. They were also compared with the work of Hummel, Sternberger, Hunscher and Macy[1] who studied a subject continuously during the last trimester of pregnancy.

Hunscher[2] and her associates have made a compilation of figures for the average retentions distributed from the third to the tenth month in 945 individual balances made on patients of various ages and on all sorts of diets in various stages of pregnancy. The means per month were 2.84, -0.15, 1.99, 2.59, 2.18, 3.23, and 3.46 gm. of nitrogen daily. While there were variations in retention on different levels of intake, negative balances predominated with intakes below 10 gm., and only positive balances were noted when the intakes were above 18 gm. per day. When these trends are compared with the results given in Table I, it is evident that the quantity of nitrogen retained by this young subject was not different from the average retained by this mixed group of individuals with their varying food intakes.

Hummel, Sternberger, Hunscher and Macy[1] made a detailed study of a woman when she was thirty-seven years old and in her fourth pregnancy. Their subject was under continuous observation during the last trimester of pregnancy and also

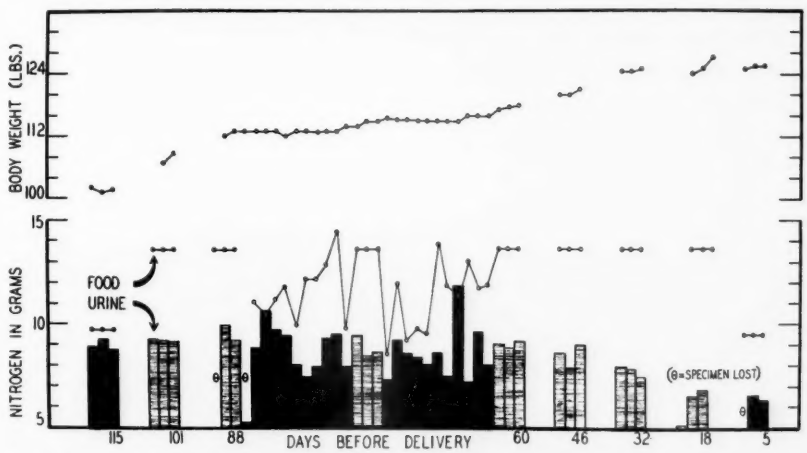

Fig. 1.—The chart shows the daily urine nitrogen excretion, food nitrogen intake and gain in body weight in the last trimester of pregnancy. The spaces between histograms merely serve to indicate that no observations were made, and have no absolute time value. The hatched histograms represent diet A.

during the lactation period. She weighed 78.5 kg. just before parturition and ate on the average of 19 gm. of protein nitrogen daily during pregnancy. Since she was heavier and consumed more protein than our subject, the comparative figures given in Table II are in terms of protein intake and retention per kg. body weight. The data of Hummel and others have been arranged in twenty-five-day averages. The figures compare as favorably as can be expected in a metabolism study of this kind, and show that the metabolism of the young individual is similar to that of the adult.

It can be seen that there was an improvement in the nitrogen balance, on diet A, with the advancement of pregnancy. If it is assumed that the digestibility of this diet was always the same, and that the somewhat variable digestibility figures are to a considerable degree due to unavoidable errors in the demarcation of the twenty-four-hour excretions, this improvement is commensurate with a decrease in urine nitrogen excretion (Fig. 1). Apparently some of the protein of this diet which is used for storage late in pregnancy is excreted as the end-product of exogenous metabolism during the period when the requirements for fetal growth are not so large. This change in the utilization of the diet is evidence that it was adequate

as a source of protein.* There were similar but less marked differences between the utilization of the self-chosen food on the one hundred and eighteenth and seventh days before delivery. Both of these last diets contained protein of good quality, but it was apparently eaten in insufficient quantity to permit optimum storage.

Although higher retentions have been found to be associated with high nitrogen intakes it is apparent from the utilization of diet A that the quantity retained by this person was more a function of time in pregnancy than of quantity ingested.† The gravid individual will, by a shift from the exogenous phase of metabolism to the growth of the fetus, store more of the nitrogen in a given diet when it is most needed if that diet is adequate to furnish the required nitrogen and energy.

Daily urinalyses were made during the three-day metabolism periods for the purpose of gaining information on the question of urine nitrogen "lag." In order to avoid a distaste for the diet, and for other practical reasons, it was desirable to have the metabolism periods of minimum length. With two exceptions, the quantity excreted on the third day compared favorably with the excretion on the second day. This fact suggests that, from the standpoint of urine nitrogen lag, one may obtain significant balance data in short metabolism periods when there is little difference between the plane of nutrition during the experimental period and that of the non-experimental period. This confirms and amplifies the unpublished data of Potgeiter and Pyle who have repeatedly used short observation periods in their metabolism studies in this laboratory.

When the subject was on the variable self-chosen diet, there was no correlation ($r = 0.04$) between food nitrogen intake and the nitrogen excreted in the urine on the same day. The lack of relationship between these two variables is also evident in Fig. 1. It must be realized that in this instance, in contrast to the three-day controlled periods, the quality of the protein has an important rôle.

SUMMARY

A fourteen-year-old human subject stored approximately the same quantity of nitrogen in the last trimester of pregnancy as older individuals do. Although her diet was the same (13.516 gm. nitrogen, or 84.5 gm. protein) for seven three-day metabolism periods, she stored more of the nitrogen in that diet toward the end of pregnancy.

Under experimental conditions the nitrogen content of a mixed human diet can be kept constant to within a coefficient of variation of 1.4.

REFERENCES

(1) *Hummel, F. C., Sternberger, H. R., Hunscher, H. A., and Macy, I. G.:* J. Nutrition **10**: 579, 1935. (2) *Hunscher, H. A., Donelson, E., Nims, B., Kenyon, F., and Macy, I. G.:* J. Biol. Chem. **99**: 507, 1933. (3) *Bethell, F. H.:* J. A. M. A. **107**: 564, 1936.

*From clinical tests it is known that this subject was anemic. Bethell[3] has emphasized that a high intake of protein of good quality is an important factor in the treatment of the anemia of pregnancy. Since this diet was eaten for only a comparatively short time one could hardly expect it to alleviate her condition.

†A few pregnant rats were fed a fixed quantity of an adequate ration daily and the quantity of urine nitrogen determined on forty-eight-hour collections. All but one refused food toward the end of pregnancy. The one successful experiment definitely showed the progressive increase in storage toward the termination of pregnancy. Although the dietary factors were equally conducive to storage at all times, the time in pregnancy was ultimately the determining factor in the quantity of nitrogen stored.

TRIPLET PREGNANCY WITH PAPYRACEOUS FETUS

SAMUEL L. SIEGLER, M.D., F.A.C.S., BROOKLYN, N. Y.

TRIPLET pregnancy is not a common occurrence. At the Brooklyn Woman's Hospital, this was the first case of triplets in over 14,000 births. By no means do all triplets survive birth and infancy.

The incidence in triplet pregnancy of the delivery at term of a live normal child, together with a macerated fetus, apparently of seven and one-half months' gestation and a mummified or papyraceous fetus approximately of eight or nine weeks' gestation, is relatively rare.

Beierlein collected 20 cases from the available literature in which there were reported triplet pregnancy with twin papyraceous fetuses. He also quotes Bertog and Maryanchik who describe triplet pregnancies with single papyraceous fetuses. Von Erlach and Sänger mention similar cases. Bretschneider observed a papyraceous fetus accompanying a premature infant and an acardiacus. Two examples of the birth of triplets, one living and the other two macerated, have been reported, one by Perdu and the other by Doesschate.

REPORT OF CASE

Mrs. E. F., aged thirty-five, para i, gravida iii, was first seen by me for this pregnancy on March 11, 1936. Past history: Hyperthyroidism in 1934 and 1935. Was treated medically with apparent good results. Still complaining of palpitation occasionally, but kept a steady weight of about 140 pounds. Basal metabolism plus 8. Hemorrhoidectomy June, 1934. Menses started at fourteen years, recurred every twenty-four days, and she bled for about five days with some clots which was usually followed by a blackish discharge for ten days thereafter. Married eight years, one spontaneous delivery in 1930, one spontaneous abortion in 1935 of a six-weeks' old gestation for which she was curetted and with no sequelae following. Last menstrual period Jan. 8, 1936. Expected date of confinement October 15.

On April 30, 7 weeks after the last menstrual period patient started to bleed which was accompanied by small clots, cramps and a chill. (She attributed this to a severe attack of sneezing.) This bleeding persisted for four days. Following this she stained for ten days, with the resultant "muddy" discharge until May 23, when she bled again for three days; this time not as profuse as heretofore, and with no clots. Rectal examination at this time showed the uterus to be enlarged to about a ten weeks' gravidity and the cervical os closed. Two units of Progestin were administered on April 30 and on May 1. The cramps subsided. Thereafter one-half unit was administered daily for the next five days, then every other day until the twenty-sixth of May. There was no further bleeding or cramps. Fetal life was felt at the fifth month.

Pregnancy continued normally until about the middle of the seventh month of gestation when patient complained of a sudden swelling of the face, hands, ankles, and an enlargement of the abdomen. Shortness of breath and palpitation were also noticed. Examinations at this time showed an edema of the parts noted together with a polyhydramnion. Only one fetal heart heard in L.L.Q. Fetus in the L.O.A. position and cephalic presentation. The vulva was considerably edematous. There was an increase in two weeks of 9¾ pounds in weight from her previous visit, from 154¼ pounds to 164 pounds. Blood pressure rose from 120/70 to 130/80;

urine negative. X-ray was suggested at this time to determine the presence of a monstrosity or multiplicity. This was refused. Thereafter, there was no further increase in weight. On October 5, at her last antepartum visit her weight was 163 pounds. Blood pressure 114/60, urine negative. Edema had not entirely subsided, hydramnion had not increased in size. Fetal heart heard in L.L.Q.; fetal parts could not be definitely made out.

Labor commenced on October 5 at term at 7 P.M. and patient was admitted to the hospital two hours later when the following was noted: Pains every two minutes, fetal heart L.L.Q., position L.O.A., membranes intact, cervix effaced, three fingers' dilated. Rectally: presenting part cephalic and engaged. Fully dilated at 9:20 P.M. Membranes ruptured and spontaneous delivery of normal female infant at 9:30 P.M. in L.O.A. position. There was a moderate amount of amniotic fluid. A few minutes later another amniotic sac appeared at the vulva, which was punctured and a profuse amount of a bloodstained fluid escaped. A

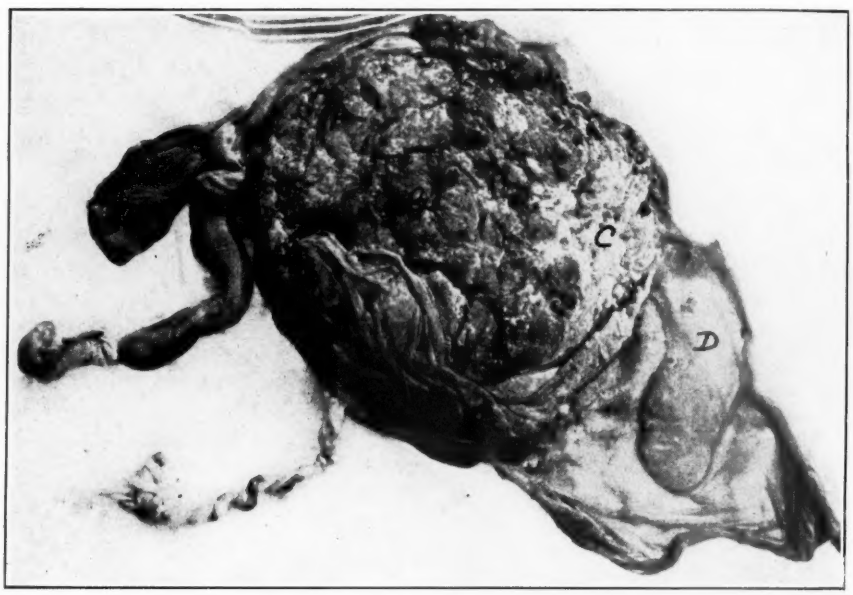

Fig. 1.

macerated fetus was extracted which presented by footling. The placenta was delivered intact. The uterus being atonic, was not firmly contracted with a resultant slow but steady blood loss. Uterus and vagina tightly packed. The shock was very profound with an imperceptible pulse and zero blood pressure readings for thirty-six hours postdelivery. During this time two transfusions of whole blood were given, 1,000 c.c. and 750 c.c. followed by a continuous venoclysis of 5 per cent glucose in saline. Oxytocics, together with the other known methods of shock treatment were instituted. Patient was discharged from the hospital on the tenth day postdelivery.

The temperature rose to 103.5° F. the first day postpartum and receded to normal on the sixth day. On discharge the uterus was well involuted. Blood pressure 114/80, pulse 90, temperature 99° F. Blood count: Hg 51 per cent, R. B. C. 2,500,000, W. B. C. 12,000; 68 per cent polymorphonuclear leucocytes, 32 per cent lymphocytes, 1 per cent eosinophiles. Urine negative.

The placenta (Fig. 1) weighed 550 gm. and measured 18.5 cm. in diameter and 2.5 cm. in thickness. It was divided into three distinct segments. An outer necrotic

surface (Fig. 1, *A*) measuring 14 cm. by 5 cm. contained many small white infarcts with a velamentous insertion of the cord. The cord measured 30 cm., was necrotic, slimy, and edematous. To this was attached the macerated fetus which weighed 730 gm. and was 25 cm. long. The center portion (Fig. 1, *B*) was 15 cm. by 12 cm. from which the outer necrotic area was separated by a distinct ridge, evidently the site of fusion of the two lobes, was normal in its appearance and consistency. The cord was centrally attached and measured 31 cm. The normal living infant weighing 2,107 gm. was 36.4 cm. long. There was a whitish, hard, fibrotic area at the other end of the placenta (Fig. 1, *C*) measuring about 3 cm. by 10 cm. from which the normal portion was sharply demarcated. Separating the layers of amnion at this end, one felt a small leathery hard mass (Fig. 1, *D*) measuring 6.3 cm. in length and 3.5 cm. in width. There was no fluid in this sac, the mass being a mummified or papyraceous fetus. Its cord, of threadlike caliber and measuring 6 cm. in length, could be seen entering the placental site at the outer edge of this fibrotic portion.

Microscopically: Extensive necrosis of the placenta comparable in appearance to an infarction. Other areas in the placenta showed scattered small foci of coagulation necrosis. Deposits of calcium were found both in the necrotic areas and also in the apparently viable villi.

There were two distinct choria and three amniotic sacs, the one chorion and its sac containing the macerated fetus, and the other chorion with its two sacs, one containing the living fetus and the other the papyraceous fetus.

DISCUSSION

From the description of the placenta herein presented, this was a case of biovular triplets, since there were two distinct choria and each of the fetuses developing in its own amnion. Still one can only tell if one is dealing with uniovular, biovular, or triovular triplets if the three were alive. Bushke states that this can only be proved by determining if they are concordant or discordant, in that there be a similarity or identity with regard to a particular phenotypic characteristic among individuals under discussion showing a definite characteristic. This, however, one could not tell in this case.

The period of development of the macerated and the papyraceous fetuses can possibly be determined in this case:

(a) By the history of bleeding in the early weeks of gestation, when in all probabilities there was an arrest in the development of one of the fetuses with the resultant mummified fetus. It is quite possible that we would have had in all likelihood an abortion of all of the nidations, were it not for the administration of the corpus luteum extract. This clinical entity should actually have been termed a missed abortion. The death of the macerated fetus occurred at about seven and one-half months of gestation, for it was at this time that the patient experienced a sudden gain of weight with the associated manifestations of hydramnion, edema, and no further gain in weight thereafter.

(b) By the roentgenograms which showed the stage of ossification of their skeletons.

In the macerated fetus there was an absence of the epiphysis of the distal ends of the femora which should be present at birth, hence placing its development at about the eighth month. In the papyraceous fetus there were noted ossifications of the ilia, scapula, long bones and the tiny centers of the phalanges with absence of the superior ramus of the ischii, placing its arrest of development at about the eighth week (Fig. 2).

However, the presence of a papyraceous fetus is certainly often overlooked, because the placenta is not always so accurately examined. Its presence is rarely of clinical importance. Sometimes a papyraceous fetus lying at the os uteri forms an

obstacle and has to be removed. More serious complications may arise if a papyraceous fetus is retained, because this may cause hemorrhages or infections during the puerperium. Its diagnosis is almost impossible unless a roentgen ray accidentally discloses the anomaly. All other symptoms which might reveal it are uncertain.

The causes of the formation of a papyraceous fetus are unknown. Many theories have been advanced. Wolff mentions disturbance of the placental circulations with predominance of the heart of one of the fetuses. Syphilis, nephritis, amniotic bridles

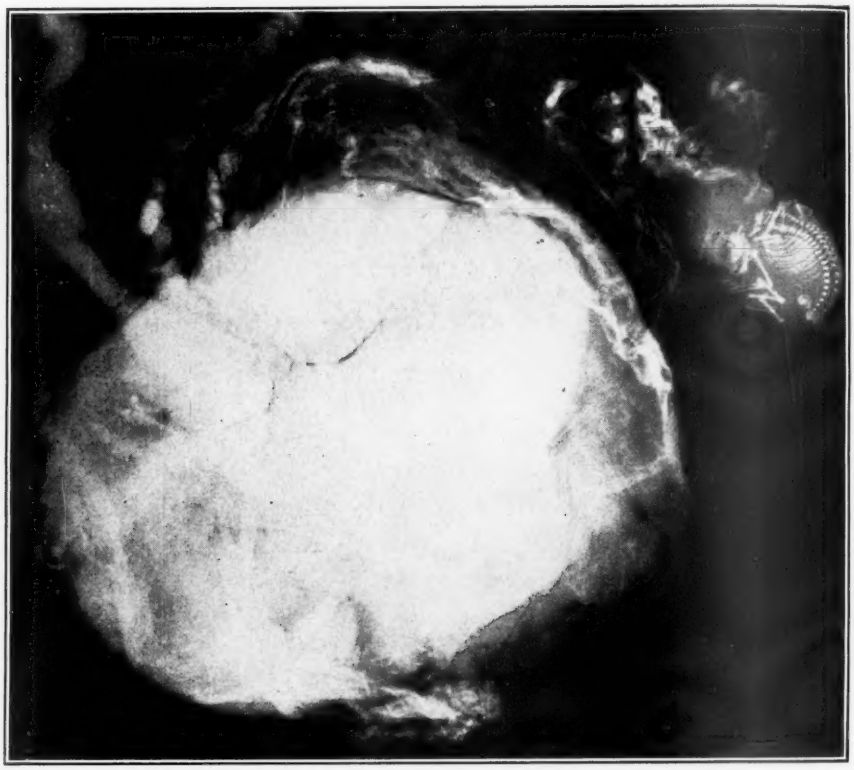

Fig. 2.

stricturing one of the umbilical cords, mechanical injuries, endometritis, etc., have been mentioned as causes. None of them was present in this case.

I wish to thank Dr. Max Dannenberg for his roentgenogram interpretations and Dr. Max Goldzieher for his microscopic pathological findings.

REFERENCES

(1) *Bumm:* Grundriss zum Studium der Geburtshilfe, ed. 11, Wiesbaden, 1917. (2) *Beierlein:* Am. J. Obst. & Gynec. **21:** 97, 1931. (3) *Von Erlach:* Zentralbl. f. Gynäk. **18:** 439, 1894. (4) *Sänger:* Zentralbl. f. Gynäk. **17:** 150, 1893. (5) *Bretschneider:* Zentralbl. f. Gynäk. **27:** 668, 1903. (6) *Perdu:* Loire. Med. **30:** 139, 1911. (7) *Doesschate:* Nederl. Tijdschr. v. Geneesk. **63:** 1357, 1919. (8) *Bushke:* J. Heredity **26:** 409, 1935. (9) *Wolff:* Zentralbl. f. Gynäk. **50:** 1313, 1926.

PHOTOGRAPHIC RECORDS OF THE CERVIX UTERI

J. M. Bruner, M.D., L. E. Rosebrook, M.D., and G. W. Cushman, B.A.,
Des Moines, Iowa

PHOTOGRAPHS of the cervix uteri are of value as permanent records of the cervix before and after such procedures as cauterization, radium application, and plastic operations. There are no good photographs of the cervix in medical textbooks or publications due to certain inherent difficulties in photography. The cervix is generally illustrated by drawings which are often inaccurate and do not present the true conditions. For these reasons an attempt was made to work out a simple technique of making good photographic records of this organ.

The two chief difficulties in photography of the cervix are proper illumination and adequate exposure. The ordinary bivalve vaginal speculum does not give satisfactory exposure. In many patients the vaginal walls are quite redundant and although the anterior and posterior walls are well retracted by the two blades of the speculum, the lateral walls fall together almost obscuring the cervix. Another difficulty is the great variation in the depth of the vagina. The direction which the cervix points, due to the position of the uterus, is also important; the cervix must be brought into a favorable position for photography.

The greatest problem, however, is illumination. It is easy to light the cervix by means of strong floodlights or mirrors outside the speculum, but photographs taken with such lighting are flat and have no detail, because the light rays are parallel to the photographic plane. The light must come from an angle, so that some degree of modeling will be produced, and the resulting photograph will possess third dimensional qualities.

For this purpose a special tubular speculum was constructed with lights incorporated within the speculum. After considerable experimentation the length selected was five inches. This was found to be long enough to expose the cervix in the deepest vagina, and in patients with a very short vagina the instrument would not protrude outside to any extent. When once introduced with the obturator in place, there was very little tendency for the speculum to be forced out of the vagina except by unusual straining. Such a speculum provides a perfectly clear round field with no interference laterally from the vaginal walls or vulva.

The cervix is engaged by the distal end of the speculum which has a ¾ inch bevel (similar to the Ferguson type of vaginal speculum). By means of the beveled end almost any cervix, no matter in what direction it points due to uterine position, can be brought into proper position for photography. Two sizes of tubular speculum were made, one 1½ inches in diameter which could be used in almost any married woman, and a larger size—2 inches in diameter which was easily introduced in women who had borne several children. This gave an excellent large field, and would accommodate the largest cervix which was encountered.

The light is furnished by two radio dial bulbs which give a brilliant light and are cheaply replaced. These are eccentrically placed on one side of the speculum, with a light shield, leaving ample room for photography. The optimum distance for the lights was found to be 4 inches; a light placed closer than this caused too deep a shadow on the opposite side of the cervix in which no detail was visible.

The secret of success for good photography of the cervix is twofold: first, the cervix itself must be deflected somewhat to one side and this is accomplished by means of the beveled tubular speculum; second, the light must be thrown on the

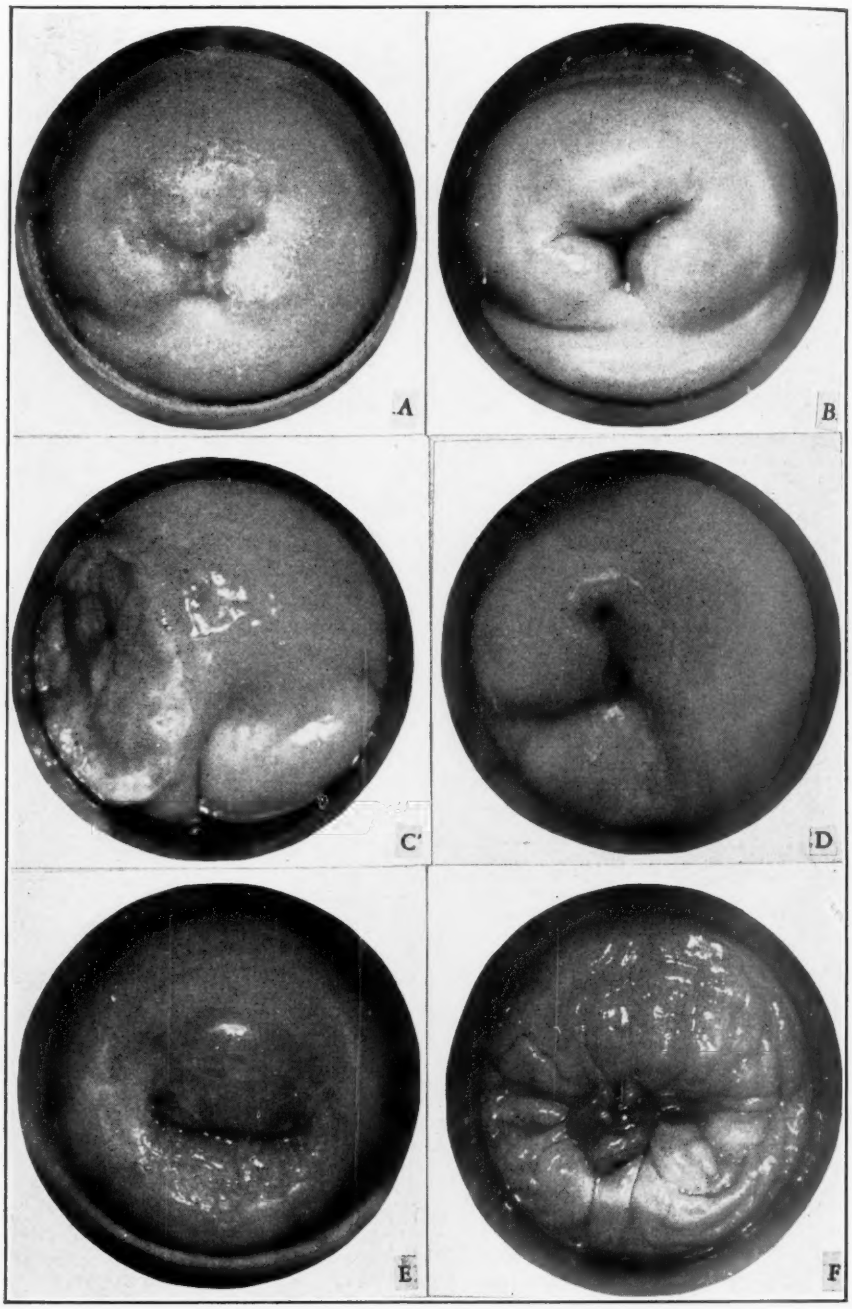

Fig. 1.—Speculum, obturator and light carrier for photography of the cervix uteri.

cervix from the quadrant opposite that to which the cervix has been deflected. For instance, the best position for the cervix is first ascertained by rotating the beveled speculum. If the cervix points posteriorly, the light carrier is rotated until the lights are in an anterior position. This provides the maximum amount of shadow effect producing black and white contrast in the photograph, and an impression of depth.

With the speculum shown here it is easy to obtain good photographs of the cervix. The patient lies on an examining table, preferably a cystoscopic table, with knee crutches. The bladder and rectum should be empty. The lubricated speculum is now introduced with the obturator in place. If necessary the gloved left hand is used to depress the perineum.

The obturator is now removed and any excess mucus or discharge removed with a few moist cotton balls. It is not advisable to attempt to remove mucus with such digestants as caroid. Any attempt to cleanse the cervix too thoroughly is likely to start bleeding.

The current, supplied by a battery of dry cells, is now turned up and the most favorable lighting of the cervix is obtained by rotating first the speculum, then the

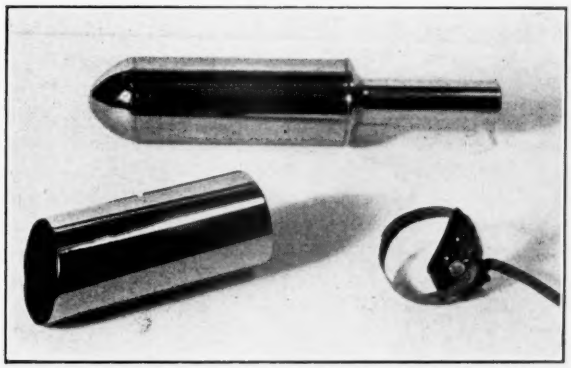

Fig. 2.—Photographs of the cervix uteri made with the equipment described. *A*, Old stellate laceration of the cervix. *B*, The same cervix six weeks after cauterization. *C*, Chancre of the lateral vaginal fornix. Positive dark-field. (Cervix pushed aside.) *D*, The same cervix eight weeks after antisyphilitic therapy. Chancre reduced to scar. *E*, Eroded cervix with nabothian cysts. *F*, Vaginal vault after vaginal hysterectomy. Granulation tissue at site of closure.

light carrier. A Leica camera on tripod is set up in front of the table, and camera lens and speculum are brought into apposition. An adjustable table is of great help in raising or lowering the hips of the patient. The camera is placed at a maximum distance from the speculum (8 to 10 inches) in order to secure the greatest possible depth of focus. The ground glass attachment for the Leica accurately defines the field and insures accurate focus. A small piece of paper with printed matter may be placed on the cervix to aid in focusing.

The patient is instructed to hold her breath at the end of expiration. (Holding the breath at the end of inspiration may force the cervix downward thus getting the subject completely out of focus.) Using Eastman "background film," the length of exposure will not be over three to five seconds. It is very unusual to have any difficulty due to movement of the patient, and very few patients complain of any sort of discomfort. Using the above method it is possible for the gynecologist to obtain good photographic records of the cervix in a few minutes' time and without undue trouble.

1005 Bankers Trust Building

ABDOMINAL PREGNANCY NEAR TERM, OPERATION AND HORMONAL STUDIES OF THE BLOOD AND URINE WITH THE PLACENTA LEFT IN SITU*

ARTHUR S. MACGREGOR, M.D., BROOKLYN, N. Y.

THE patient, who was thirty-four years of age and of Italian extraction, was admitted to the Norwegian Hospital on Nov. 18, 1935. Her physician had advised hospital care because of the severity of nausea, vomiting, constipation, and painfulness of fetal movements.

Her past history aside from her menstrual, marital, and obstetric history was irrelevant. Her menses began at thirteen, occurred regularly at twenty-eight-day intervals and were of four-days duration, being associated with moderate dysmenorrhea. She had first married in 1919 and two pregnancies occurring shortly thereafter were terminated by induced abortions at three months and apparently were not followed by sepsis. After living with this husband for two years she divorced him and remarried in 1924. She did not conceive again until 1929 at which time a left salpingectomy was performed for a ruptured ectopic gestation. There were no pregnancies from then on until the one under consideration.

The last menstrual period began on March 15, 1935 at the expected date and was normal in all respects. About four weeks later she began to spot and experienced cramplike pain such as she would have during her periods. This spotting and pain continued for the next two weeks, the bleeding on one occasion amounting to a definite flow for several hours. There was no further bleeding during the remainder of the pregnancy. Pain along the entire right side of the abdomen and chest was present at intervals associated with attacks of weakness. The pain was often relieved by enemas. Nausea and vomiting were a prominent symptom throughout, the patient losing eighteen pounds in weight. Constipation was a persistent symptom also. In the last trimester the fetal movements caused the patient great distress in the upper abdomen.

I first saw her in consultation on November 27, three and one-half weeks prior to her estimated date of confinement. The patient was found to be a poorly nourished individual with a diminished hemic component, who did not appear well. Her temperature was 98.2° F., pulse 85, respirations 20, and blood pressure 116/76. Physical examination revealed no abnormalities aside from evidences of weight loss, the breast signs of pregnancy and the abdominal findings.

The abdomen was greatly enlarged as though by a twin pregnancy. What first appeared to be the fundus uteri was found to be 27 cm. above the symphysis, and there seemed to be a marked widening of the upper portion of the abdomen. Palpation revealed, however, that the child was in the upper abdomen lying transversely with the head on the left side just beneath the costal margin. The fetal parts were unduly prominent. The right lower quadrant of the abdomen was occupied by a semisolid fixed mass with a rounded upper edge which extended upward to slightly above the umbilicus and appeared to arise from the pelvis. This mass seemed to fuse with another mass which was also present in the lower abdomen to the left of the first mass extending over into but not completely filling the left lower quadrant and rising to the level of the umbilicus. The fetal heart was heard in the upper left quadrant. On vaginal examination the cervix was found high up

*Presented at a meeting of the Brooklyn Gynecological Society, April 2, 1937.

on the left side of the pelvis. The right fornix was filled by a rounded semicystic mass of large size which was continuous with the masses felt abdominally. The cervix was soft but not patulous or effaced. An x-ray examination made at eight months revealed that the child was lying directly transverse in the upper abdomen with the head on the left side. The child did not seem enclosed by a shadow such as it would be were it intrauterine. The grotesque sprawled out positions of the extremities are not seen in uterine pregnancies. R. B. C. 3,500,000; Hb 69 per cent. The white cell count was 7,500 with 80 per cent polys. The urine was negative except for a trace of albumin. The blood chemistry report was nonprotein nitrogen 28.7 mg., urea nitrogen 11.3 and glucose 89 mg. Operation was decided upon a week later because of the patient's suffering, and because it was felt that the baby was large enough to be viable.

On December 3 abdominal section was done under ether anesthesia. At this time the patient was about two and one-half weeks from term. An incision was made over the right rectus muscle about an inch to the right of the umbilicus, one-third of the incision being above and two-thirds below the umbilicus. The rectus muscle was retracted outward and the peritoneum incised. The omentum was found to be adherent to the anterior abdominal wall throughout the lower half of the incision. These adhesions were cut and the bleeding points in the omentum ligated. The omentum was drawn up and the pelvis explored. The uterus was found to be soft and enlarged to the size of a five to six months' gestation. It was pushed to the left by a mass about 25 by 10 by 10 cm. in size. This proved to be the placenta which was attached to the posterior surface of the right broad ligament extending downward into the culdesac and outward to the lateral pelvic wall. Fine adhesions between the appendix, cecum, small intestine and the maternal surface of the placenta had to be freed before the full extent of the placental attachment could be determined. The cord was found to emerge from deep in the pelvis and the placental site extended from the culdesac up over the pelvic brim. There was no evidence of the membranes except over the maternal surface of the placenta and no fluid was present in the abdomen. The right tube could be traced for a distance of about four inches when it seemed to fuse into the placental mass. It was flattened and about one-half inch in width. The child was found to be lying transversely in the upper abdomen beneath the omentum, transverse colon, and stomach. It was extracted by the feet and breathed immediately. The child was found to have a calcaneus deformity of the right foot and asymmetry of the head, thorax, and abdomen of a moderate degree. The birth weight was 2,660 gm. The cord was cut and ligated close to the placenta. No attempt was made to separate the placenta from its attachment. The abdomen was closed in layers without drainage.

The patient had an extremely mild postoperative febrile reaction. There was practically no abdominal distention at any time nor was there any vomiting. On the twelfth day a few drops of serum were evacuated from the incision which otherwise healed by first intention. The patient was kept in bed until the twelfth postoperative day and was discharged on the nineteenth day. At the time of discharge the placental mass filled the right lower quadrant of the abdomen extending upward to the level of the umbilicus. The uterus was undergoing moderately rapid involution, being the size of a five to six months' gestation at the time of operation and nineteen days later but little more than half that size. During her hospital stay there was no uterine bleeding noted. On the fourth and fifth days the breasts which had remained flaccid, were pumped to stimulate lactation. There was no milk secretion present and the breasts never showed any signs of engorgement during her hospital stay or subsequently. On January 8, thirty-five days after the operation, slight spotting occurred and persisted for three weeks. The patient had a month of amenorrhea and since then has menstruated every twenty-four to twenty-seven days, having moderate dysmenorrhea similar to what she previously

had. Eight weeks postoperatively the placental mass had diminished but slightly in size but the uterus had almost returned to normal size. Examination sixteen months after the operation still revealed the presence of the mass in the right side of the pelvis. It was about the size of a large orange and was found to be partially fixed to the side of the pelvis. The uterus was normal in size and partially mobile. The patient stated that never at any time since leaving the hospital had she had any discomfort. The baby has had the calcaneus deformity corrected and aside from slight asymmetry of the head appears normal in all respects.

It was felt that it would be interesting to make a survey of the hormone content of the blood and urine in this case. Through the kindness of Drs. Frank and Goldberger this was done at the Mt. Sinai Hospital.

The blood taken on the second day following operation gave a full estrogenic reaction in 40 c.c. of blood as in normal pregnancy. A week later on the ninth day the reaction was negative in this quantity of blood. The first urine on the second day gave a positive Friedman test with 0.75 c.c. of urine which corresponds to 1,333 rabbit units per liter. On the fifth day the urine showed only 50 rabbit units per liter while subsequent Friedman tests were negative on the tenth, seventeenth, and twenty-fourth postoperative days. It was determined that the estrogenic reaction in 40 c.c. of blood became negative between the second and ninth days and that the prolan titer in the urine diminished rapidly, becoming insufficient to produce a positive Friedman test on the tenth day. From these studies it would appear that the placenta ceased producing prolan and estrin in appreciable amounts within less than ten days after the operation.

Ware and Main[1] reported a very similar case of abdominal pregnancy in which the placenta was not removed. Nineteen Friedman tests done during the first thirty-five days after the operation were all positive, the first negative being obtained on the thirty-sixth day. Three others done shortly thereafter were also negative. Halban in 1905[2] was the first to note that lactation was inhibited by the retention of the placenta and that it occurred usually about three days after the removal of the placenta. Frank[3] describes a case in which the placenta was retained in utero for fourteen days with lactation following its removal in three days. Riddle[4] isolated the hormone prolactin from the anterior lobe of the pituitary in 1932. The weight of experimental evidence today makes it appear that estrin and possibly progestin prepare the breasts for lactation and that prolactin may be the activator of or, at least, is responsible for the continuance of lactation.

Estrin has been found to inhibit lactation as has to a lesser extent the anterior pituitary-like substance. The occurrence of lactation has been attributed to the removal of these two hormones from the blood circulation. In the case reported it would appear that these two hormones disappeared rather quickly from the maternal system and yet lactation did not occur. I can offer but two explanations for this. One, that this patient's anterior pituitary gland may have been deficient in prolactin production or second that in cases of retained placenta some factor other than the continued production of estrin and prolan inhibits the action or production of prolactin.

REFERENCES

(1) *Ware, H. H., Jr., and Main, R. J.:* Am. J. Obst. & Gynec. **27**: 756, 1934. (2) *Halban, J.:* Arch. f. Gynäk. **75**: 353, 1905. (3) *Frank, R. T.:* Endocrine Aspects of Gynecology, Nelson Loose Leaf System. (4) *Smith, O. W., and Smith, G. Van S.:* Am. J. Obst. & Gynec. **33**: 365, 1937. (5) *Riddle, O., Bates, R. W., and Dykshorn, S. W.:* Proc. Soc. Exper. Biol. & Med. **29**: 1211, 1932.

141 Joralemon Street

ACTINOMYCOSIS OF THE OVARY*

FREDERICK H. FALLS, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, University of Illinois, College of Medicine, and the Gynecological Service, Cook County Hospital)

ACTINOMYCOSIS of the ovary is a relatively rare disease. Haselhorst up to 1928 collected 60 cases. Only three primary ovarian cases have been reported. The cases are usually secondary to bowel, lung, or head and neck infections.

None of the patients in the 60 cases reported by Haselhorst recovered permanently. Schugt reported an unusual case of a patient in 1930 who had an infected abortion four years previously with slow recovery. She developed a tender mass in the region of the right ovary which was drained vaginally and was then treated by x-ray. About twelve weeks later the left tube and ovary became involved in a similar process and was drained in the same manner. This was followed by x-ray therapy and the patient was well one year later at the time of the report.

Most of the reported cases have been noted in the right ovary, although the left ovary may become secondarily infected. It is probably very rare that infection spreads from the uterus, cervix, or tube to the ovary, although the possibility cannot be denied. The spread from the gastrointestinal tract is much more probable, and according to more recent investigators, may be associated with the fact that these organisms have been found in the human mouth around carious teeth.

The probability that the organisms occur in grasses and grains is remote, since the organism does not form spores and is not resistant to heat, cold, or drying.

Pathologically, the organism produces a granulomatous change in the ovarian tissue which eventually breaks down to form pus containing the characteristic sulphur granules. The condition cannot be recognized clinically from other pelvic infections until it has progressed to the stage of pus formation. The diagnosis is never made clinically pre- or postoperatively until the chronic sinuses form, from which cultures can be made from the sulphur granules. By the time the diagnosis is made the process is so far advanced that hope of complete removal of the infection is remote. This probably accounts for the unfavorable results obtained in the cases reported to date. Serum agglutinations give confirmatory evidence but are not dependable.

Cornell collected 71 cases up to 1934. Of these 45 died, 8 were improved, 7 the outcome is doubtful, and only 11 are possible cures. He reports one case with a four-year cure. The infection involved both tubes and ovary. Bilateral salpingo-ovariectomy was done, patient was treated subsequently by potassium iodine. Of the 71 cases 50 involved the tube and ovary.

Schiller reported a fatal case in June, 1913, which was not included in Cornell's group. Since then Coté and Tudhope have reported 4 fatal cases of ovarian actinomycosis.

CASE REPORT

The patient, a forty-three-year-old colored woman born in Alabama, entered the Cook County Hospital on the Obstetrical Service, Mar. 9, 1936, complaining of pain in the right lower quadrant for ten weeks and amenorrhea for two months. Her last period began Dec. 30, 1935. On Jan. 1, 1936, a dull aching pain started in the right lower quadrant, and was continuous. She was treated conservatively

*Presented before the Chicago Gynecological Society, March 19, 1937.

and at the end of the month, Apr. 8, 1936, was taken to the operating room and an exploratory operation was performed. A large inflammatory mass was found which was thought to be too acute to remove and the abdomen was closed. The patient was instructed to return in six months for further surgery. She lost sixty pounds in weight during her stay at home.

The old wound appeared well healed and a large firm mass filling the pelvis and extending upward to the level of the umbilicus was found to the right of the midline. The lower abdomen was tender. The cervix was tender, movable, and took the Schiller stain well. Pelvic abscess was diagnosed, probably encapsulated in a tube or ovary because of the hardness and lack of fluctuation. Operation Oct. 22, 1936. Right-sided large tuboovarian abscess found with marked adhesions and pelvic peritonitis. Left adnexa normal.

Technique: Abscess was aspirated and most of the pus evacuated. Abscess sac was raised with difficulty from the culdesac and removed. Hemorrhage was slight and easily controlled. The wound had to be reopened about the fifth day and about three ounces of pus was removed. The wound then healed rapidly and the patient left the hospital Nov. 8, 1936. Cultures from the wound were negative for actinomyces. The report on the pathological specimen by Dr. Jaffe is as follows:

"The specimen consists of a mass 10 cm. in diameter; surface is deeply injected; on sectioning it contains a cavity 8 cm. diameter filled with a bloody material; wall is up to 20 mm. thick. Microscopic: The ovarian tissue is practically completely replaced by a granulation tissue surrounding multiple abscesses. A portion of an old corpus albicans is noted. Numerous giant cells are seen throughout the granulation tissue. Here and there typical clusters of ray fungi are noted. No tubal tissue is seen."

The patient was referred to the Research Hospital for deep x-ray therapy. She has regained 27 pounds in weight and feels fine. Small sinuses in the abdominal wound are still draining.

She has received four treatments of 325 r. units each between Feb. 16 and Feb. 24, 1937. These were applied anteriorly and posteriorly on the right side alternating. Each of these treatments is equal to a half of a skin erythema dose.

The patient had very little reaction to the x-ray, and is now getting potassium iodine ten drops three times a day, and increasing one drop each day. Further x-ray treatments are to be given, and because of the frequency of the infection to the opposite tube and ovary as noted in several cases in the literature, the left adnexal region will be x-rayed prophylactically.

REFERENCES

(1) *Haselhorst:* Arch. f. Gynäk. **134:** 561, 1928. (2) *Schugt, P.:* München. med. Wchnschr. **77:** 394, 1930. (3) *Colebrook, L.:* System of Bacteriology. Relation to Medicine **8:** 78, London, 1931. (4) *Cornell, V. H.:* Am. J. Path. **10:** 519, 1934. (5) *Schiller:* Monatschr. f. Geburtsh. u. Gynäk. **38:** 367, 1913. (6) *Coté, F. H., and Tudhope, G. R.:* J. Path. & Bact. **42:** 673, 1936.

1819 West Polk Street

OVARIAN PREGNANCY*

A. E. KANTER, M.D., F.A.C.S., CHICAGO, ILL.

(From the Department of Gynecology of the Mount Sinai Hospital)

MRS. F. T., thirty-six years of age, was first seen on Jan. 6, 1937. She had been married for thirteen years and had been pregnant for the first time ten years ago when she aborted spontaneously at two months. Her last regular menstrual period occurred on May 25, 1936. On August 2, nine weeks after that period, she began to experience cramping pains in the lower abdomen. One week after this she began to bleed from the vagina, passing a small amount of blood constantly for a period of ten weeks after which there was a spontaneous cessation. Since that time the patient has remained in bed in order that the pregnancy might be retained. On November 28 the patient again began to pass blood from the vagina in small amounts, a condition that persisted until she was admitted to the hospital. During this entire period of time the patient had a poor appetite and as a result had lost thirty pounds.

General history was entirely irrelevant as was the general physical examination. Past history revealed that the patient had had attacks of tonsillitis, whooping cough, spastic colitis, and psoriasis. The menstrual history preceding the present difficulties was of no import, the periods having recurred at regular intervals and having been of average length. At the time of admission to the hospital the temperature was 97.8° F., pulse rate 72, respiratory rate 20, and blood pressure 108/76. The examination of the blood revealed a hemoglobin content of 75 per cent (Sahli), 3,390,000 red blood cells and 6,750 white blood cells with a differential count within normal limits. An Aschheim-Zondek test in November, 1936, was reported as positive.

On Jan. 4, 1937, the fetal heart sounds being absent, the patient was taken to the hospital in order that termination of the pregnancy might be accomplished. X-ray examination revealed a fetus that was projected over the upper cecal region and which was markedly smaller than was consistent with the period of amenorrhea.

At 10:00 P.M. of that day the patient was taken to the delivery room for the purpose of introducing a Voorhees' bag. It was found that the cervix could not be dilated sufficiently to allow for this procedure so a gauze pack was inserted into the cervix and vagina.

I first saw the patient on the morning of Jan. 6, 1937, at which time a bimanual examination revealed a cystic mass in the abdomen reaching just above the level of the umbilicus. The uterus was not enlarged over normal, was pushed over to the left by the abdominal mass, and the left vaginal fornix was thus obliterated. The uterus and cervix presented a firmness which is not ordinarily associated with pregnancy. A diagnosis of abdominal pregnancy was made and immediate laparotomy advised.

Abdominal section was performed on Jan. 6, 1937. Upon opening the abdomen it was found that the uterus was pushed over to the extreme left and was the size of a six weeks' pregnancy. There was a swelling the size of a large football, starting from the uterine horn on the right and extending behind the uterus, filling the entire pelvic area. Attached to the upper and lateral part of the mass was the sigmoid and small bowel. The mass was apparently an ovarian pregnancy with secondary rupture into the abdominal cavity. The sac was opened and a dead five

*Presented before the Chicago Gynecological Society, March 19, 1937.

months' fetus was removed, following which the mass was brought up and removed by means of clamps. A portion of the sac was left attached to the sigmoid. Peritonization was accomplished with the round ligament to the right horn of the

Fig. 1.—Chorionic villi in ovarian tissue.

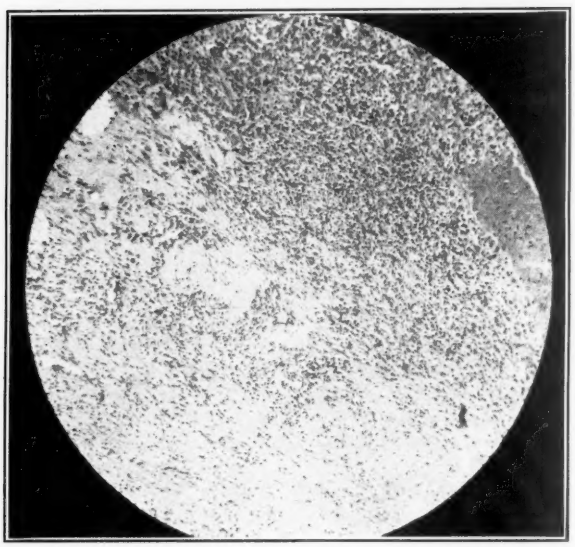

Fig. 2.—Decidual reaction and necrosis in ovary.

uterus. The right tube was normal and was not involved in the ovarian mass. The abdomen was closed without drainage.

After a slight rise in temperature during the first four days after operation the patient had an uneventful postoperative course and was discharged from the hospital on Jan. 15, 1937.

The pathologist's report as submitted by Dr. I. Davidsohn was: "Ovary: Specimen has the shape of a globular mass that has become deformed by a deep laceration. The outer surface shows some smooth areas, but in the most places there are evidences of loose recent adhesions. The color is pinkish red, purplish, and black. The consistency is quite soft. The whole specimen measures 14 by 11 by 8 cm. Enclosed within it is a cystic and partly opened cavity. One of its walls is made up by the bulk of the already described ovarian tissue. The other walls are considerably thinner and in the preserved portions measure from 1 to 8 mm. The inner surface of this cavity has an irregular and nodular appearance. Apparently a part of the cyst wall was left behind in the abdominal cavity. Attached to the inner surface is a thin membrane measuring about 11 by 5 cm. which has the appearance of a portion of fetal membranes. Section surface of the thickest portion of the wall is very hyperemic. It shows numerous hemorrhages. Separated from this specimen is an amorphous piece of tissue measuring 80 by 40 by 40 mm., having the identical structure as the main specimen. A nodule 20 by 12 mm. of a firm consistency and dark brown in color is present. It is 10 mm. long and has a thin pedicle. On section surface it shows, in the center, a brown amorphous tissue. A male fetus measuring 23 cm. having a macerated skin and being in a state of advanced decomposition is present. The cord measures 27 cm. and shows no gross abnormalities.

"*Microscopic:* Sections from the different portions of the specimen show decidual and placental tissue with extensive areas of necrosis and diffuse hemorrhages. At the periphery a narrow strip of connective tissue is present. In others ovarian tissue is present with some hyalinized areas and a great deal of blood pigment.

"*Diagnosis:* Ovarian pregnancy."

310 South Michigan Avenue

Di Gioia, A. M.: Studies of the Difficulties Encountered in the Friedman Test, and a New Modification Using Blood Serum, J. Lab. & Clin. Med. 22: 508, 1937.

The Friedman test has been reported as being practically infallible after the tenth day following the first missed period following suspected conception. But there have been many difficulties encountered in carrying out the test, the two important ones being shock following injections of urine and false negative or positive reactions. Shock following injection of urine may be due to too rapid injection, the taking of large doses of aspirin or quinine by the patient, inbreeding of rabbits, and extremely acid or alkaline urine. The reaction of the urine should have a pH which ranges from 6.8 to 7.4. False negative or positive reactions may be due to urine specimens obtained within a period less than ten days following the first missed period, in which case the pituitary hormone may not be excreted in sufficient quantity. The urine of patients having certain types of tumors (chorionic) may contain gonad-stimulating hormones.

To overcome these difficulties, Hoffmann's modification has been proposed. This consists in the withdrawal of 25 c.c. of patient's blood, centrifuging the specimen, and injecting 10 to 13 c.c. of the serum into the marginal ear vein of the rabbit. The rabbit may be autopsied within twenty-four hours. No figures are given, but it is hoped that this modification will supplant that in which urine has heretofore been used.

W. B. Serbin.

INTESTINAL OBSTRUCTION COMPLICATED BY PREGNANCY AT TERM*

RALPH A. REIS, M.D., CHICAGO, ILL.

FEW reports have been published of intestinal obstruction occurring in the second half of pregnancy or at term. There is a small number of reports of ileus occurring late in pregnancy but mechanical obstruction is most uncommon. Cornell,[1] Lazard,[2] Charbonnet,[3] and Massey[4] have reported mechanical obstruction in late pregnancy; in each of these instances, the obstruction was produced by an omental band or an adhesion, the freeing of which resulted in a return of intestinal integrity.

The following case is of interest because the intestinal obstruction had resulted in a gangrene which necessitated the excision of more than 200 cm. of ileum, immediately following a Porro cesarean section. There is apparently no similar case reported in the recent literature.

Mrs. E. W., a thirty-one-year-old primigravida, whose last menstrual period was on June 6, 1935, was first seen on March 1, 1936. She complained of generalized cramplike, abdominal pains which had been present for one month, and of excruciating abdominal pain associated with nausea and vomiting for the past twenty-four hours. This severe pain was rhythmic, cramplike, occurred every ten to fifteen minutes, and lasted thirty to sixty seconds. These severe pains, which were generalized at first, localized in the right lower quadrant after about eight hours. She had had two similar attacks before the onset of her pregnancy and one such attack, but without nausea or vomiting, about four weeks before the present one. At this time she had been given morphine for the pain which had been diagnosed as gallbladder colic. Her previous history included a curettement and laparotomy for the removal of a uterine tumor and relief of uterine bleeding eight years previously.

Examination showed a patient writhing with abdominal pain, hiccoughing constantly, and complaining of recurrent nausea with occasional vomiting. Her color was good, the pulse was 80 and good quality, temperature 98.6° F. Abdominal examination revealed generalized tenderness most marked in the right lower quadrant, the point of greatest tenderness being about two inches above the umbilical level on the right side. Rebound tenderness was also marked on the right side, as was rigidity of the rectus muscle. The uterus was of a size corresponding to a thirty-eight weeks' pregnancy, was firmly contracted, with no periods of relaxation and was very sensitive to the touch. The fetus was lying in cephalic presentation and the fetal heart tones were strong and regular. Blood examinations showed no anemia and a leucocyte count of 13,400; examination of the urine showed no abnormalities. The patient was given a one-quart soap-water enema with no results.

The preoperative diagnosis was generalized peritonitis with intestinal obstruction due to appendicitis or postoperative adhesions. Gastric lavage was done, a dark fecal-like fluid being obtained. Ten per cent glucose solution was given intravenously, normal saline solution subcutaneously, and the patient was prepared for operation. The abdomen was opened by a paraumbilical right rectus incision, and about 50 c.c. of a turbid fluid was found in the peritoneal cavity. On drawing the gravid uterus forward into the incision, it was found that the entire posterior and right surfaces of the uterus were covered by densely adherent coils of small intestine, the majority of which were gangrenous. A cesarean section was then

*Presented before the Chicago Gynecological Society, March 19, 1937.

performed through a fundal incision, a normal healthy male child being delivered. The dense adhesions between bowel and uterus were dissected free. It was then found that the uterus, even though empty, was of a size which would prevent adequate exposure of the involved bowel and mesentery; a supracervical hysterectomy was therefore done.

Examination of the gangrenous bowel showed the involvement to be confined to the ileum. About 175 cm. were definitely gangrenous and the mesenteric vessels contained multiple emboli which involved apparently normal bowel on either end of the gangrenous portion. About 15 cm. of healthy bowel at each end was therefore included in the resection, 205 cm. of bowel being included. The intestinal continuity was re-established by a side-to-side anastomosis. The patient left the operating room in critical condition with a marked degree of shock.

The pathologic report was as follows: "The specimen consists of 205 cm. of small intestine. The serosal surface of one portion is dull, granular, and greenish red. Fifty centimeters from one end, firm adhesions bind neighboring loops of intestine. The lymphatics are markedly distended. The mucosa of the most distal portion is smooth and gray pink in color. Nine centimeters from the distal end, a sharp line separates this mucosa from a neighboring granular, raised, gray green red mucosa covered by necrotic membranous material. Fifty centimeters from the proximal end of the specimen, a line sharply separates darker gray black mucosa from the uninvolved portion. The greatest circumference of the bowel is 9 cm. The attached mesentery is hemorrhagic and thrombosed."

The postoperative course was most stormy, the temperature ranging from 101° to 104° F. for six days and pulse varying from 120 to 160, with a very low tension and of poor quality. During this time, a Wangensteen tube was in place constantly, continuous intravenous glucose was administered and the patient was given three transfusions of 500 c.c. each of whole blood on alternate days. The patient had a spontaneous bowel movement on the third day and thereafter had two to four small liquid bowel movements daily. On the sixth day, the Wangensteen tube was removed, fluids administered by mouth. The temperature reached 101° F. for twenty-six days after which it remained normal. A suppurating wound infection developed on the eighth day which drained spontaneously and continued to drain until the twenty-seventh day. The patient was discharged on the thirtieth day.

She has subsequently enjoyed good health, her only complaint being frequent small bowel movements with occasional, slight, momentary cramps. Tests of the intestinal motility show this to be more rapid than normal.

REFERENCES

(1) *Cornell, E. C.:* Surg. Clin. N. A. **12:** 1253, 1932. (2) *Lazard, E. M.:* Am. J. Obst. & Gynec. **26:** 462, 1933. (3) *Charbonnet, P.:* Ibid. **29:** 591, 1935. (4) *Massey, W. E.:* Texas State J. Med. **31:** 566, 1936.

104 South Michigan Avenue

Lucchetti, Giovanni: Triple Diagnostic Error in a Case of Pregnancy Complicated by Fibroid of the Uterus, Clin. ostet. **16:** 520, 1936.

The author presents a case of pregnancy complicated by fibroid of the uterus in which were committed three diagnostic errors. The first error was made when the diagnosis of an ovarian cyst was made and disproved at operation. The second error was the failure to recognize the fibroid of the uterus. The third error was made when the fibroid was mistaken for a second fetus, revealed when the patient delivered only one fetus.

August F. Daro.

ABERRANT SUPRARENAL GLAND TISSUE IN THE BROAD LIGAMENT*

JAMES A. GOUGH, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, St. Luke's Hospital)

THE suprarenal gland, according to Goldzieher† develops from two primitive layers, the cortex from the mesoderm, the medulla from the sympathicus structure of the ectoderm. The medulla is formed from islands of cells originating from the sympathoblasts, later clumping together to form a definite layer in the mature organ. Isolated groups of medullary cells at times persist to form the so-called bodies of Wiesel and of Zuckerkandl.

The cortical cells spring from the "interrenal zone" of mesodermal epithelium lining the celome prior to segmentation. This zone extends from the glomus of the pronephros to the cloaca. Clumps of these cells proliferate, become pedunculated, separate from the celomic epithelium, and then coalesce to form the "interrenal organ," the precursor of the cortex of the suprarenal gland. Fusion of the medulla with the cortex occurs about the middle of the third month of intrauterine life. Many of the interrenal elements do not participate in the formation of the cortex but remain isolated, later undergoing regressive changes and finally disappearing. Persistence of such cell buds in postfetal life accounts for the so-called accessory suprarenal glands or Marchand's adrenals. In as much as only cortical cells are present, these names are misleading.

They occur most commonly in the vicinity of the adrenals, the kidneys, about the ovaries, testicles, broad ligaments, epididymis, and in the inguinal canals. The frequency with which they are found seems to vary with the type of observation. Anatomists state that they are very common, but clinical reports are decidedly infrequent. In *The Quarterly Cumulative Index Medicus* from 1932 to 1936, inclusive, the titles of only ten articles bearing on this subject are found.

M. A., a white woman, aged thirty-five years, and married fourteen, was admitted to the service of Dr. C. F. G. Brown at St. Luke's Hospital, Chicago, April 2, 1935. She complained of chronic indigestion characterized by anorexia, nausea, constipation, and abdominal discomfort of several years' duration; she said that she was nervous and slept poorly.

She had had two term pregnancies, one twelve, the other seven years before admission, both terminated by cesarean sections in another city. A thyroidectomy had been done in 1926. The family history was not significant. Menstruation had begun at the age of fifteen, had always been regular, of five days' duration, recurring every twenty-eight days, and occasionally painful.

General examination revealed a poorly nourished woman, extremely myopic, and weighing only ninety-three pounds. Her systolic blood pressure was 108/68. Examination of the chest, including a roentgen film, was negative. The abdominal wall was very thin, and an old lower left rectus scar was visible; no masses were palpable. Vaginal examination revealed no abnormal findings except the presence of a large amount of bowel in the culdesac. A blood count, including a differential,

*Read before the meeting of The Chicago Gynecological Society, March 19, 1937.

†The Adrenals, Their Physiology, Pathology and Diseases. Goldzieher, Max A.: New York, 1929, The Macmillan Company.

was entirely normal. Examination of several specimens of urine revealed a few red and white blood cells in the sediment. A kidney function test was normal, likewise an intravenous pyelogram.

The patient was anxious to be sterilized, and in view of her poor health, this seemed imperative. Accordingly, on April 17, 1935, under ethylene anesthesia, the abdomen was opened through a lower midline incision. Except for a marked ptosis of the stomach and intestines, no gross pathologic findings were noted. On the free edge of the right broad ligament midway between the uterus and the pelvic wall a tiny white object was seen. This was about a millimeter in diameter; at first it gave the impression of lying free in the peritoneal cavity, but was then found to be pedunculated. There was no surrounding inflammatory reaction. It resembled a healed tubercle or material encysted by the peritoneum. Slight capillary oozing followed its removal. Both tubes were ligated and cut and the abdomen closed

Fig. 1.—Cross-section showing suprarenal gland tissue. ×45.

in the routine manner. The postoperative course was uneventful, the patient leaving the hospital eighteen days after the operation.

The following report is by Dr. Edwin F. Hirsch, Attending Pathologist at St. Luke's Hospital:

"In Zenker's solution is a tissue 3 by 2 by 1 mm. It is encapsulated, and has the structure of the cortex of the suprarenal gland. Fine fibrous strands extend from the capsule and separate cords of large cells with a foamy and granular cytoplasm. The cells are arranged as in the zona fasciculata. Best's carmine stain demonstrates the presence of a small amount of glycogen substance in the cytoplasm of the cells. The fibrous capsule is about 0.5 mm. thick, and outside of this is a little fatty areolar tissue. There are no inflammatory exudates."

A small mass of tissue discovered accidentally in the broad ligament proved to be a remnant of interrenal gland tissue with a structure corresponding to the cortex of the suprarenal gland.

ERYTHROBLASTOSIS FETALIS AS A CAUSE OF INFANTILE MORTALITY*

A Preliminary Report

Carl T. Javert, M.D., New York, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

THE present study is based on 10 cases which have been observed at the Woman's Clinic. Time does not permit a detailed report. Therefore, these remarks must be construed as a preliminary report. Studies are now in progress, and will form the basis of a subsequent communication.

The maternal records may be summarized as follows: The mothers averaged thirty-one years in age. Mediterranean ancestry was noted in 50 per cent of the cases. Multiparity was present in 9 cases. No familial incidence of the disease was observed. The Wassermann was negative in all. The hemoglobin averaged 83 per cent. Pregnancy was complicated by a poor weight gain in 50 per cent of the cases, and suggests a nutritional basis. An achlorhydria was found in one case so studied. The duration of pregnancy ranged from thirty-four to forty weeks with an average of thirty-seven weeks, indicating slight prematurity. Analgesia was used in 4 cases, and nitrous oxide anesthesia in 8 cases. Labor was short with an average duration of nine hours, of which the second stage was less than one hour. Delivery was spontaneous in 7 cases. Fetal distress was observed in 3 cases; 2 of which occurred in the second stage, while nitrous oxide was being administered. Both of these infants were delivered with forceps in order to obtain a living baby, but to no avail. The amniotic fluid had an amber color in 4 cases. A presumptive diagnosis of erythroblastosis was made before delivery in one case, and this case will be reported at a later date.

The placentas averaged 775 gm. in weight, which is about one-sixth heavier than normal. The fetal surface was distinctly yellow in 3 cases. On histologic section, erythroblasts were found in the fetal vessels.

The infants' records will now be reviewed. The sexes were about equal. The average weight was 3,457 gm. (7.5 pounds), which is excessive for infants of thirty-seven weeks' gestation. The edema and fluid in the serous cavities added to the increased weight. Resuscitation was necessary in 50 per cent of the infants. The rôle of analgesia and anesthesia in producing asphyxia can only be inferred. Edema was

*Read at the Section of Obstetrics and Gynecology, New York Academy of Medicine, January 26, 1937.

noted in 3 cases, icterus in 5, pallor in 4, dyspnea in 6, and cyanosis in 5 cases. Convulsions were present in 3 cases, and a heart murmur in 2. Skin petechiae were frequently observed, and bleeding from the mouth and rectum was seen in 2 cases. The liver and spleen were usually enlarged.

The lowest red cell count was 1,300,000 per c. mm., with an average for the group of 3,400,000. The average hemoglobin was 51 per cent. The color index was 1.5. The nucleated elements ranged from 23,000 to 256,000 per c. mm.; of which 6 to 362 per cent were nucleated red cells.

The mortality was 70 per cent. The treatment was repeated transfusions. The 3 patients that survived received 9, 7, and 4 transfusions, respectively, in the first days of life. Within two weeks, the nucleated red cells had disappeared. These infants are now living and well. In England, Hampson uses human blood serum intramuscularly, with a mortality of only 6 per cent.

Autopsies were performed in 7 cases. The liver and spleen were invariably enlarged because of the hemopoietic hyperplasia. All patients showed an enlargement of the heart, and no cause for the cardiac murmur was found. Fluid was often present in the serous cavities, particularly in the pleural space, thereby contributing to the dyspnea and cyanosis. Petechiae were frequently observed on the mucosal and serosal surfaces. In the 3 patients that had convulsions, 2 had subarachnoidal hemorrhage, and the third had "kernicterus."

To recapitulate, erythroblastosis runs part of its course intra utero, and is recognizable at birth. The obstetrician is in a strategic position for diagnosis. His suspicions are aroused before delivery by the racial aspects, and a history of familial jaundice. A poor weight gain and an achlorhydria may also be premonitory. Hydramnios may be present. Diminished or absent fetal activity is suggestive. Fetal distress may occur. The amber-colored fluid when the membranes rupture is important. After making a presumptive diagnosis of erythroblastosis in the unborn child, all analgesia is interdicted, although rectal ether without quinine may be used for fetal distress. At the time of delivery, no nitrous oxide should be administered. Open drop ether may be used, although no anesthesia is preferred. The diagnosis is established after delivery by the deep yellow vernix, or the presence of hydrops. A palpable liver and spleen are confirmatory. The increased size of the placenta, with a yellow fetal surface or an edematous appearance, is additional evidence. Erythroblasts in the blood smear, and in the fetal capillaries of the placenta, complete the diagnosis.

Other conditions must be differentiated. Prematurity is associated with an increased number of nucleated red cells. Sepsis and congenital syphilis must be considered. The skin petechiae may lead to an erroneous diagnosis of hemorrhagic disease. The collapse and cyanosis suggest

intracranial hemorrhage. The heart murmur presupposes a congenital lesion. The jaundice may lead to a conclusion of malformation of the biliary system. Aplastic anemia and leucemia must also be ruled out.

The incidence of erythroblastosis at the Woman's Clinic in 1936 was 1 in 400 infants. However, a study of the infantile mortality reveals even a greater incidence. Stander has advocated that all infants weighing over 1,500 gm., regardless of maceration or deformity, and those dying within the first fourteen days of life, be included in the total infant mortality rate. Of 110 infants so classified, 5 or 4.5 per cent were due to erythroblastosis. In the same year, 3 deaths were attributed to syphilis. Therefore, erythroblastosis exceeds syphilis as a cause of infantile mortality.

In conclusion, may I add that obstetricians are in a strategic position for the management of this condition, so that the present high mortality rate can be lowered appreciably.

REFERENCES

Arey, L. B.: Developmental Anatomy, Philadelphia, 1934, W. B. Saunders Co., p. 280. *Ballantyne, J. W.:* Diseases of the Fetus, Edinburgh, 1898. *Bloomfield, J. E.:* Brit. M. J. **1:** 1142, 1901. *Cooley, T. B., et al.:* Am. J. Dis. Child. **34:** 347, 1927. *de Lange, C.:* Jahrb. f. Kinderh. **114:** 15, 1926. *Diamond, L. K., et al.:* J. Pediatrics **1:** 269, 1932. *Ecklin, T.:* Monatschr. f. Kinderh. **15:** 425, 1919. *Hampson, A. C.:* Lancet **1:** 429, 1929. *Parsons, L. G., et al.:* Arch. Dis. Child. **8:** 159, 1933. *Pehu, M., et al.:* Bull. Acad. de méd., Paris **114:** 820, 1935. *Pfannenstiel, J.:* München. med. Wchnschr. **57:** 397, 1910. *Rautman, H.:* Beitr. Path. Anat. **54:** 332, 1912. *Schridde, H.:* München. med. Wchnschr. **57:** 397, 1910. *Stander, H. J.:* Am. J. Obst. & Gynec. **28:** 421, 1934. *Strauss, M. B., and Castle, W. B.:* New England J. M. **207:** 55, 1932.

525 East Sixty-Eighth Street

DISCUSSION

DR. ARTHUR M. REICH.—The condition of erythroblastosis fetalis may recur in more than one offspring from a particular mother, as was demonstrated in a case of a colleague of mine. This patient had her first labor sixteen years ago, resulting in a normal living child. The second baby had hydrops and died in the first days. Then there were three babies in successive confinements, all showing similar findings and results, namely, icterus of the newborn and death on the third day of life.

Five years ago this same woman was attended in her sixth confinement by my aforementioned colleague who had not attended her before, but was acquainted with the previous history. He had an immediate diagnosis made by a blood examination on the newborn child. A transfusion was performed at once, followed by subsequent transfusions. The baby recovered.

DR. JAVERT (closing).—There have been no cases of familial occurrence in our series, although there are descriptions in the literature, particularly by de Lange, of several instances of hydrops and icterus gravis in successive infants born to the same mother.

UNILATERAL GONORRHEAL SALPINGITIS IN BICORNUATE UTERUS

H. C. James, M.D., Tucson, Ariz.

UNILATERAL salpingitis in a bicornuate uterus is apparently a rather rare condition. The case which I am reporting at this time occurred in a girl thirteen years of age and was accompanied by a pelvic cellulitis with abscess formation in the posterior culdesac.

CASE HISTORY

Miss M. M., aged thirteen years, came to the office on May 26, 1936, with a chief complaint of vaginal discharge of about two months' duration. The onset was gradual and was not associated with pain. There was, however, a frequency of urination noted with the onset. The rest of the history of the present illness and the history by systems was of no consequence. Menstrual periods began when she was eleven years old. The periods were always regular, twenty-eight days apart, and lasting five to seven days. The flow was rather profuse but not associated with pain, backache, or headache. Last menstrual period May 16, 1936.

Past History.—Patient had pertussis at age of three years, otitis media at fifteen months, and the left ear has drained at irregular intervals ever since. She is deaf in the left ear. She had a tonsillectomy at twenty months and has had a scoliosis of dorsal spine since two years of age.

Physical Examination.—On inspection of the patient I was impressed with the precocious secondary sexual development, also the low tone quality of the voice. Her height was 57¾ inches, weight 94 pounds. Skin showed acne of face and neck. Her teeth were carious. Her thyroid was palpable, smooth and diffusely enlarged. There was a marked kyphosis and left scoliosis of spine with wasting of muscles of left shoulder. Her breasts were large, but there was no discoloration of nipples and no secretion present. Heart and lungs negative. Abdomen: short type with flare of ribs at the epigastrium; no pain nor tenderness. Pelvic examination showed introitus to be of the marital type, admitting 2 fingers with ease. There was a profuse foul vaginal discharge, greenish in color and rather thick in consistency. On entering the vagina there was a large fluctuating mass extending from under the symphysis to the posterior fornix on the left side. The mass was not particularly painful. It was impossible to outline the uterus and on speculum examination the cervix was very difficult to find; when found it revealed the point of exit of the discharge.

Laboratory Studies.—Blood, Kahn and Wassermann, negative; count normal; urine negative; smear: mixed bacteria—no gonococci.

On May 27, 1936, a posterior colpotomy was performed under nitrous oxide oxygen anesthesia and about 500 c.c. of foul smelling, thick, tenacious pus was obtained. Two Penrose drains were inserted. On June 3, 1936, all drains were removed. The discharge had stopped. Patient had no elevation in temperature and felt fine. Pelvic examination at this time revealed an irregular painless movable mass on the right side of the pelvis. It was decided at this time to follow with a course of Elliott treatments for a week to see what improvement or change would occur. At the end of one week there was no change and laparotomy was advised.

On June 17, 1936, under nitrous oxide ether anesthesia an exploratory laparotomy was performed. At operation a bicornuate uterus was discovered, with marked thickening and inflammation of the left tube, the tube being about the size of a thumb. The right tube was normal in appearance. The left tube was removed. The appendix was slightly inflamed, and it also was removed. Smear made from pus in left tube reported as positive for gonococci.

The patient made an uneventful recovery until July 21, 1936, when it was discovered that the abscess in the posterior culdesac had re-formed. This was opened through the old incision and about 2 ounces of thick creamy pus was obtained. This wound continued to drain until Aug. 24, 1936, when the patient was last seen. At that time there was no discharge. Pelvic examination was negative and the patient felt fine.

AN AID IN THE STUDY OF STERILITY

ROY E. KRIGBAUM, M.D., F.A.C.S., COLUMBUS, OHIO

THOUGH most of the steps in the analysis of an individual case of sterility can be easily carried out in the physician's office, one offers especial difficulty, namely obtaining an adequate and undeteriorated specimen of the posteoital contents of the vagina. Ordinarily the physician resorts to one of three measures: He may call at the patient's home to secure the sample; he may provide in his office facilities for the intercourse of patient and husband and then proceed with his examination; or he may make an office examination of the patient after intercourse at home, with some loss of the contents by gravity during the trip.

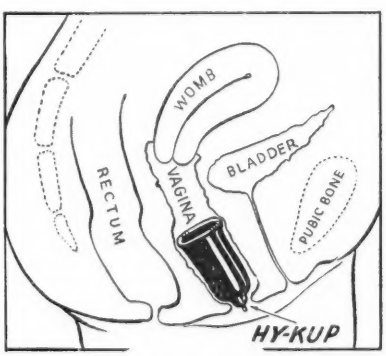

Fig. 1.

In an effort to escape the inconveniences of the first two measures and the impracticality of the third, the author has found what has proved in practice to be an ideal and simple solution—the employment of a bell-shaped rubber cup* originally devised for insertion into the vagina during the menstrual period. This device is 2¼ inches in length, 1½ inches in outside diameter, and has a capacity of 30 c.c. It is soft and pliable and may be folded between thumb and forefinger for insertion. Upon its introduction into the vagina it resumes its original shape and adheres to the walls, forming an effective seal by suction. An elongated tip on the closed end

*_Hy-Kup_—The Hy-Kup Distributors, Indianapolis, Indiana.

facilitates removal. It is free from any chemical compounds destructive to the sperm, such as are often found in condoms, and it may be boiled to insure perfect sterilization.

The procedure with the patient is as follows: She is carefully instructed in the method of inserting the cup and cautioned to sterilize it in boiling water prior to her use of it at home. It should then be wrapped in a clean handkerchief and laid near at hand for insertion immediately after intercourse. After she has adjusted the cup she is ready to come to the office for postcoital study. Two hours is suggested as the maximum interval between intercourse and the patient's arrival for examination. The patient is then put on the table and the cup removed by the physician. The postcoital contents are found to have been held in situ and intact, and abundant samplings can now be taken under optimum conditions to determine the number and motility of the sperm cells at various levels of the vagina and cervix, the presence or absence of pus cells, and the presence or absence of any cervical secretions destructive to the sperm.

This procedure has been used by the author over a period of four years and has been found uniformly satisfactory. It insures first of all a very adequate and fresh sampling of the postcoital contents and has as well the great advantage of saving the physician annoyance and time and the patient embarrassment and extra expense.

276 East State Street

Robertson, Edwin: A Study of the Contractions of the Nonpregnant Human Uterus, Edinburgh M. J. **44**: 20, 1937.

The results obtained with the intrauterine balloon method of recording contractions of the nonpregnant human uterus in the living subject show spontaneous activity of the uterus at various times from the beginning to the end of the menstrual cycle.

The results also show that in 11 out of 12 women, tested in the second half of the menstrual cycle, posterior pituitary extract caused increased muscular activity of the uterus.

Wm. C. Henske.

Renton, Harold: Vaginal Discharge, South African M. J. **10**: 808, 1936.

The author discusses the normal mechanism for the maintenance of vaginal acidity. The intricate power of the ovaries to effect changes in the glycogen content of the vagina and the ultimate production of lactic acid through the action of the Döderlein's bacillus are pointed out.

Pathologic discharges are primarily the result of infection. The organisms are usually of a mixed type—staphylococci, streptococci, coliform bacilli, and diphtheroids are the most common. Gonococcal and parasitic infections are separate entities. The trichomonas is the most common parasite producing discharge.

Frequently a virginal noninfective leucorrhea is present. A hormonal disturbance may be the basis for this.

Trichomonas vaginalis is described, as well as methods for examining and staining the parasite. Treatment for leucorrhea is outlined.

F. L. Adair and S. A. Pearl.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MARCH 4, 1937

The following papers were presented:

A Case Report of Solitary Endometrial Cyst of the Sacrouterine Ligament. Dr. S. Leon Israel.

Report of a Visit to Middlesex Hospital, London, Eng., and to the Radium-hemmet in Stockholm, Sweden. Dr. Brooke M. Anspach.

The Use of Diathermy in Gynecologic Out-Patient Clinic. Dr. Edward F. McLaughlin.

Experience in the Treatment of Carcinoma of the Fundus of the Uterus With Five Year End-Results in Forty-Seven Patients. Dr. Lewis C. Scheffey and Dr. William J. Thudium. (For original article, see page 1006.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MARCH 19, 1937

The following papers and discussions were presented:

Intestinal Obstruction Complicated by Pregnancy at Term. Dr. Ralph A. Reis. (For original article, see page 1038.)

Ovarian Pregnancy. Dr. A. E. Kanter. (For original article, see page 1035.)

Biology of the Human Vagina in Pregnancy. Dr. M. Edward Davis and S. A. Pearl. (To be published.)

Actinomycosis of the Ovary. Dr. Frederick H. Falls. (For original article, see page 1033.)

Aberrant Suprarenal Gland Tissue in the Broad Ligament. Dr. James A. Gough. (For original article, see page 1040.)

Pseudohermaphroditism. Dr. H. O. Jones.

Multiple Carcinoma Occurring in Two Patients. Dr. Fred O. Priest.

Bone Changes in the Fetus Following the Administration of Dicalcium-Phosphate and Viosterol to the Pregnant Woman. Dr. G. C. Finola, et al. (For original article, see page 955.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF MARCH 5, 1937

The following paper was presented:

The Stillbirth Problem. Dr. Philip F. Williams, of Philadelphia (By invitation). (For original article, see page 940.)

MEETING OF APRIL 2, 1937

The following papers were presented:

Abdominal Pregnancy Near Term, Operation and Hormonal Studies of the Blood and Urine With the Placenta Left in Situ. Dr. A. S. MacGregor. (For original article, see page 1030.)

The Theca, Granulosa, Lutein Cell Tumors of the Human Ovary and Similar Tumors of the Mouse's Ovary. Drs. H. F. Traut and J. S. Butterworth. (For original article, see page 987.)

Editorial

Factors Responsible for Failure Further to Reduce Infant Mortality

THE first report of a survey by the Board of Health of Chicago of the deaths of infants less than thirty days of age was published during the summer of 1936.* From this report Bundesen and his coauthors concluded that efforts to reduce neonatal mortality must be centered upon the control of the causes of death at the time of birth of premature babies. A new report† somewhat modifies this conclusion and lessens the stress laid upon simple prematurity. Attention is now drawn to the difficulty of attacking the problem of neonatal death, when the relative frequency of the different causes of death in this period is so little known. Ordinary statistics frequently misrepresent the true importance of various special causes. These errors result partly from the rather rigid classification imposed by the *International List* and the *Manual of Joint Causes,* and partly from the fact that the statistics are usually based on groups of cases, a large proportion of which have not been subjected to competent postmortem examination.

The rules of the official classification result particularly in many deaths being classified as due to prematurity when they are actually the result of other causes. Thus, when 1,123 neonatal deaths were officially classified, 44.6 per cent were assigned to premature birth; while among 398 deaths studied by satisfactory necropsies, there were only 82, or 20.6 per cent, in which the only known factor responsible for death was the prematurity. With this reduction, as the result of postmortem examination, in the importance of simple prematurity as a cause of death, there occurred a definite increase in the frequency of intracranial hemorrhage, a slight increase in congenital malformations, and a tripling of the relatively infrequent deaths from pneumonia.

The comment is rightly made that before procedures can be effectively carried out to reduce the number of deaths in the neonatal period, the causes of these deaths must be accurately determined. This can be done only by large series of competently performed autopsies and by a system of classification which will bring out the essential point in the loss of each infant.

*Bundesen, H. N.; Dahms, O. A.; Frohbein, W. I.; and Harmon, G. E.: Mortality of New-Born Infants in Chicago during 1935, with Special Reference to the Premature, J. A. M. A. **107**: 270, 1936.

†Bundesen, H. N.; Frohbein, W. I.; Dahms, O. H.; and Potter, E. L.: Factors Responsible for Failure Further to Reduce Infant Mortality, J. A. M. A. **109**: 337, 1937.

After reading these excellent reports, one is struck by the pertinence of the conclusions in two respects. For the individual obstetrician nothing is more valuable than to see the ill effects of his own unsuccessful operation. The demonstration of intracranial hemorrhage and tears of the tentorium or falx after a forceps delivery or a broken neck after a breech extraction cannot fail to impress the operator with his responsibility. Such mental acceptance of responsibility is far too easily avoided when the death can, without necropsy, be assigned to such "natural causes" as asphyxia or atelectasis. From a constructive viewpoint visualization of the mechanical effects of traumatic procedures will go far toward teaching the operator what modifications he must make in the mechanics of his own technique of delivery.

The wider point brought out is that without accurate statistics the campaign against neonatal deaths is without definite objectives. To obtain such statistics there must be more necropsies and a revision or rejection of the official rules for classification of the causes of death in this group of cases. This calls first for coordinated efforts on the part of hospitals to supply data from sufficiently large groups of necropsied cases and, second, for action by some suitable body concerned to agree on a better system of assigning causes of death in the neonatal period. The latter may be the proper work of a Board of Health or of one of the national medical societies.

In spite of technical difficulties in the collection of accurate statistics, the investigators permit themselves certain definite conclusions that their investigations to this point have led them. This study has shown that four main causes which contribute greatly to infant death are: (1) maternal complications, such as a toxemia and placenta previa, for such maternal complications were present in 385 out of 1,123 neonatal deaths; (2) inexpert obstetric care, for cerebral hemorrhage was the most frequent cause of death (25.6 per cent) in the infants upon whom necropsies were performed; (3) prematurity; (4) incorrect or inadequate neonatal care. With these causes the obstetrician will in general agree, although he will certainly plead that the full quota of cerebral hemorrhages be not assigned to "inexpert obstetric care."

Emphasis may shift with the changes in the system of assigning causes of death, but with these studies the general direction of attacking the problem of neonatal deaths is indicated. The work of the Chicago investigation is most important. It deserves to be copied and to receive whatever cooperative support is needed.

Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D.

Collective Review

MENSTRUATION AND ITS DISORDERS

A Critical Review of the Literature from 1933 to 1936 Inclusive

Hugo Ehrenfest, M.D., St. Louis, Mo.

(Concluded from page 729, October Issue.)

XII. MENARCHE

Newer investigations in regard to age of menarche and the various factors which determine the appearance of the first menstrual flow vary in their results. Engle and Shelesnyak[257] found that of 250 Jewish girls in a New York Orphan Asylum by far the larger percentage had their first flow in the winter months, while amenorrheas will occur more often in the summer months. According to Ishizaka[258] also among Japanese girls, the menarche most often appears in the cold winter months, as a rule at an earlier age in those living in cities. The same facts were ascertained by Yosioka[259] who studied 1,172 Japanese college students. December showed the highest incidence of first menstrual flows. Most extensive statistical researches, covering all parts of Japan, made by Tomii,[260] in contrast tend to prove that first menstrual flows most often appear in the spring, the least often in winter.

Chinese statistics, presented by Yang and Gear,[261] are based on the study of 2,924 girls. In about 58 per cent of them, menarche occurred in spring or summer, and at a considerably earlier age than among European people. Investigating Polish women in Wilno, Luczynski[262] found that in Jewish girls the menarche occurred about one year earlier than in non-Jewish women, in his opinion, expressing the great importance of the factor of race, and the unimportance of environment. Skerlj[263] claims that Norwegian statistics support the idea that menarche is influenced by climate, a view practically identical with that given by Arescheff[264] after a study of menarche in Armenian girls.

Kennedy's[265] conclusions are drawn chiefly from notations found on the hospital records of 10,000 female patients. The age of menarche for Edinburgh is not significantly different from that reported from Italy or Russia. Figures from Prussia, however, give a decidedly higher average age, and those from Rio de Janeiro, on the other hand, are much lower. In his opinion, it can be deduced that climatic differences probably are inoperative but that environmental agencies apparently play a rôle. No correlation was found by him between early or late menarche and high or low fertility.

In the opinion of Peller,[266] a recognized authority in biometric statistical studies, climatic influence certainly is smaller than commonly considered to be. The psychic factor is of considerable importance and excitement over a birthday celebration in all probability accounts for the rather frequent appearance of the first menstrual flow on a birthday or at least within the month of the birthday. Obviously such a psychic factor can become operative only if the development of the genital sphere is sufficiently advanced to permit such a reaction to an emotional stimulus. The physical development in its last analysis, however, is greatly affected by such external conditions, as environment, food supply, place of living, work, and state of health.

Among the diseases of childhood which retard menarche, Dworzak[267] assigns first place to rachitis. For this reason women with a late menarche show so high an incidence of pelvic anomalies. Also Tranquilli-Leali[268] claims that, in most women, whose menarche occurred too early or rather late, the pelvis will be found to be abnormal. Weysser[269] refers to Feldweg's earlier report that women with earlier or unusually late menarche in large numbers develop menstrual disorders or have pathologic deliveries. Weysser can only confirm this observation as far as pathologic labors are concerned. He made also the following differentiation: Difficulties of labor in women with delayed menarche were found to be due to pelvic anomalies, while in those with early menarche, the difficulties were due rather to abnormal resistance of the soft portions of the birth channel. A control study, very recently reported by Risopoulos,[270] fully confirms Weysser's finding in regard to the relation of late menarche to obstetric complications, but fails to support his claim regarding an effect of early menarche on the soft tissues of the lower birth canal. Weysser in his conclusions stresses the significance of constitution in the age of menarche.

The rôle played by constitutional variations in the occurrence of menarche and menopause is most interestingly discussed by Julius Bauer.[271] In the germ plasm of the fertilized ovum are determined the chief characteristics of the life of an individual and with them the rate of his evolution and involution. But obviously, environmental factors in this respect will exert some influence at some time or another. The causes for the menarche thus are genotypically fixed, but alterations are possible through the harmful effect of intervening disease on the various endocrine elements which conjointly lead to sex maturity. Involution of ovarian activity can be entirely independent from the general phenomena of senescence.

Very similar ideas are expressed in Ploss-Bartels *Woman.*[195] The earliest available material led us to suppose that climate and especially temperature were the main factors in retarding or hastening the first menstrual period, but all newer material leaves no doubt that these influences are rather unimportant in comparison with those of the internal secretions, food, habits and manner of life, and racial stock. Social class and habitat are closely related to early or late sexual stimulation and experience, but the internal glands determine constitutional variations of different "endocrine blends" (Mathes). They are expressed in such opposite types as "pyknic" or "asthenico-ptotic," the latter being the more common in women with menstrual disorders.

Most convincingly Breipohl[272] shows that all scientifically valuable investigations on menarche must be based on data more reliably pro-

cured than heretofore. Information obtained from patients or their parents rests solely on usually inaccurate memory. In his opinion, the best method in this respect is the one officially introduced in Koenigsberg. Every school teacher is required to make a record of the exact date when one of her little pupils has her first menstrual flow.

As a valuable statistical study we may quote one made by Petri.[273] He collected data from large families with several female children. Thus he could make comparisons between the ages of menarche of the mother and all her daughters. Comparative investigations were also made between various groups of girls, even on 100 pairs of female twins. In all the different groups, outside of twins, the average age of menarche varied within so wide limits that the strikingly small variations in the 51 pairs of uniovular and 47 pairs of biovular twins must be accepted as pointing clearly to a definite causal relationship between hereditary factors and time of sexual maturation.

An instance of unusually early menarche is reported by Stiasny.[274] Menstrual flows began at the age of one year. When two and one-half years old, the child had well-developed breasts, pubic hair on the mons veneris, and fully developed external genitalia. At that time, she flowed regularly every four weeks. Mayer's[133] statement that precocious menarche often impairs later development and reduces survival chances is in accord with the known fact that premature ovarian activity rather frequently is directly due to some complicating pathologic condition.

Kraus[275] deals with the frequently reported association of hydrocephalus with sexual precocity. He investigated the relation of increased intracranial pressure to disturbances of the pituitary gland. It seems that in patients with neoplasms of the brain or meninges, or in patients with chronic internal hydrocephalus the anterior lobe of the pituitary becomes either underactive or overactive, depending on the particular changes in the hypothalamic region.

In a discussion of granulosa cell tumors of the ovary, characterized by production of large amounts of estrogenic substances, Novak and Gray[276] refer to the fact that precocious menstruation may be due to various endocrine anomalies. Its occurrence in association with a palpable ovarian tumor should always lead to the suspicion of a granulosa cell tumor. Bland and Goldstein[277] made hormonologic studies on a child, six years old, with precocious sexual development. The latter finally was definitely traced as due to bilateral granulosa tumors. They found 8 similar reports to date in the literature.

The first bio-assay of estrogen hormone contents of a granulosa cell tumor has been reported by Gospe.[278] He found 3.2 M.U. per gram of fresh tumor tissue and 36 M.U. per gram of desiccated tissue. Naturally these findings do not express the actual capability of this tumor to produce estrogenic substances. Occasionally they exert a luteinizing effect and cause amenorrhea as shown by Benda and Kraus.[278a]

XIII. DELAYED MENARCHE—PRIMARY AND SECONDARY AMENORRHEA

It is more convenient to discuss delayed menarche, primary and secondary amenorrhea together, because these three anomalies of menstruation have many causative factors in common and call for rather similar therapy.

It is common practice to speak of *delayed menarche* if the first menstrual flow has not appeared at an age of about sixteen, and to diagnose

primary amenorrhea if the still amenorrheic woman is older than eighteen. No agreement exists in regard to a clinical differentiation of a long interval menstruation from a *secondary amenorrhea.*

Newer literature on either delayed menarche or primary amenorrhea deals chiefly with such causes as underdevelopment of the uterus, noninitiation of ovulation, and failure of the endometrium to pass through the typical changes of the cycle. They all are dependent more or less directly on abnormal (not necessarily deficient) activity of various endocrine glands and not solely of the ovaries.

With the present acute interest in the physiology and pathology of the endocrine system and the great faith in the therapeutic efficacy of hormone extracts, medical literature of the past few years abounds in reports concerning scientific investigations of the complex interrelations between the entire endocrine system and menstrual function (estrus in various animals), and contains many, more or less reliable, clinical contributions describing results (chiefly good) obtained with certain organ extracts in the treatment of the various disorders of menstruation.

These introductory remarks seemed necessary to explain why the following pages present a survey of only a relatively small part of this literature. We attempted to select only those papers, experimental and clinical, which can be considered of theoretical and practical interest and value to the practicing gynecologist. Since many of them discuss etiology and therapy of all types of disordered menstrual function, it was at times impossible to limit quotations to those dealing specifically with amenorrhea.

Disordered menstrual function, as a matter of fact, is but a symptom complex and, therefore, its appropriate treatment necessarily is determined by the exact diagnosis of the underlying cause which in itself (e.g. deficient ovarian endocrine function) may represent only the effect of still another cause (e.g. abnormal activity of another endocrine gland). As emphasized, among others, by Benthin[279] the task of discovering the basic etiology in the individual case is a very difficult one. The attempt to fit all these varying primary and secondary causes into a comprehensive and presumably useful schematic arrangement inevitably becomes a very complex problem as can be gleaned from the tabulation offered, e.g. by Crossen and Crossen.[280] Many writers are willing to agree (e.g. Josef Novak[281]) that in a large number of amenorrheas the true cause cannot be discovered. Even the most elaborate classifications obviously cannot solve the problem of correct diagnosis, because, e.g. in amenorrhea, such vague factors as change of domicile (girls entering college or training schools for nurses), chilling, emotional shock, etc., admittedly play an important rôle. Mascaretti[282] describes a hysterical woman who periodically becomes amenorrheic whenever she thinks that she is pregnant. Literature contains many reports of such imaginary pregnancies even associated with secretion of true milk in nulliparous women (as I observed in one of my patients). As previously mentioned, Theobald[66] ascribes anomalies in the rhythmicity of the menstrual function to functional disorder of a special center in the hypothalamus controlling periodicity. Kreis,[19] who believes in an independent rhythmicity of endometrial changes, logically concludes that oligomenorrhea or amenorrhea cannot be accepted as proof of an existing ovarian deficiency, that even under these conditions the ovulation process may proceed normally. Also Robert T. Frank[49] states that

amenorrhea, oligomenorrhea, and functional bleeding of any sort are unreliable as positive indices of ovarian function.

Almost two decades ago German medical literature extensively discussed the many unaccountable aspects of the so-called "War amenorrhea." This particular form has disappeared since then, and its place in Germany, at the moment, is taken by another inexplainable amenorrhea, succinctly termed by Nordmeyer and Howe[283] the *Landjahr Amenorrhea.* It occurs in young girls between fourteen and fifteen years old who, on account of impaired health or solely "for the purpose of protecting them against politically dangerous surroundings," after graduation from public schools, are systematically removed, for approximately eight months, from the larger cities to rural districts to become familiarized with agricultural life and work. Investigations have revealed that, within one large group, out of the 89.6 per cent of girls menstruating regularly at the beginning of this service, only 27.3 per cent were still regular at its termination. Of the 10.4 per cent menstruating irregularly at the start, all with the exception of one had become amenorrheic, which together with temporary or complete cessation of flows during the time of service brings the total of amenorrheic girls in the entire group at the end of the *Landjahr* to 64.9 per cent, with about three-fourths of them not having menstruated since admission to the service.

Comparisons with groups of girls assigned to other types of work lead the writers to the conclusion that the only cause for this amenorrhea could be the fact that they were living in a special part of the country under a particular climate. They feel that there is every reason to assume that this unfavorable effect is only temporary and will not affect later menstrual or reproductive function of these girls. However, it seems pertinent to mention in this connection a recent paper of Wehefritz and Gierhake,[284] in which they discuss the present, striking prevalence in Germany of uterine hypoplasias. They arrive at the conclusion that a steadily increasing incidence of uterine hypoplasia, usually ascribed to ovarian deficiency, can be satisfactorily explained only on the basis of deficient diet in the post-war period when these women were approaching puberty. In the light of recent information, it seems likely that an insufficient amount of vitamins in this respect played the most important part.

It is generally appreciated that secondary amenorrhea frequently appears as an early sign of tuberculosis. Therefore, the careful physical examination required in every case of interruption of heretofore regular menstrual function must include a study of the lungs. Gal,[285] contrary to prevailing views, believes that the amenorrhea in these patients is caused not by the disease or a tuberculous toxin, but more likely is due to a pathologic constitution which predisposes the woman to a tuberculosis infection. In some tuberculous women, the amenorrhea may be the result of destruction of endometrium or ovaries, involved in the process. Gal concludes that in the majority of these patients it will hardly be necessary to attempt restoration of the menstrual function by endocrine or any therapy. Kriech[169] goes even farther. He states that the use of ovarian preparations to counteract menstrual disorders in tuberculous women frequently aggravates the tuberculous process.

The complexity of relationship between amenorrhea and ovarian function is clearly evidenced by a report of Stein and Leventhal[286] in which they describe cure of amenorrhea in seven cases by means of resection of bilateral, small cystic degenerated ovaries. As is well known, small cystic degenerated ovaries, almost characteristically, cause profuse bleeding from a hyperplastic endometrium, developed under overstimulation by an excess of estrogenic substances originating in the many small cysts, all lined by granulosa cells. Stein and Leventhal account for amenorrhea in association with polycystic ovaries and for the good results secured with resection in the following manner: Small cystic degeneration of ovaries is induced by an excess of anterior pituitary hormones. The amenorrhea is due to mechanical conditions within the ovaries. Crowding of the ovarian cortex by the cysts interferes with maturation of the small follicles which are pressed down deep into the ovarian substance.

Much interest has lately developed concerning the endocrine activities of certain ovarian newgrowths. We have previously spoken of the estrogen producing granulosa cell tumors which may lead to precocious menarche. Another type of ovarian tumor, in accord with Robert Meyer's suggestion generally termed arrhenoblastoma, is characterized by masculation (i.e. defemination) of the patient. The earliest symptoms comprise lengthening of the menstrual intervals until amenorrhea is established, accompanied by atrophy of uterus and breasts. Then follow changes in all the secondary sex characteristics to those of the male. In women, below the climacteric age, removal of the newgrowth causes gradual subsidence of virilism with restoration of normal menstrual function. Even instances of subsequent pregnancies have been reported. Recurrence of the neoplasm again causes masculation of the patient. An exhaustive survey of the literature on arrhenoblastoma recently has been published by Fauvet.[287]

Also the adrenal cortex produces a hormone which is of importance in the development of the secondary sex characteristics. With certain tumors of the adrenal glands hirsutism and amenorrhea develop regularly. Thus, as pointed out by Saphir and Parker,[287] the symptoms of an excess of adrenal cortex hormones are practically identical with those of an arrhenoblastoma. These writers report a case of typical adrenal virilism in which the adrenals were found to be seemingly normal, but aberrant adrenal cortex tissue was discovered in an ovary. They state that increased adrenal cortex function seems to be associated with increased excretion of estrogenic substance in the urine, a fact seemingly contradicting prevailing conceptions but theoretically explainable.

Ever since the classic researches of Leo Loeb, it has been known that a persistent corpus luteum (or corpus luteum cyst) inhibits ovulation and causes amenorrhea. Therefore, we wish to mention in this connection the statement of Hamblen and Ross[288] that administration of the anterior pituitary-like luteinizing factor may cause degenerative processes in the ovaries, seemingly often resulting in formation of follicle cysts and persistence of the corpus luteum. They add that these changes possibly are only temporary and thus do not represent a permanent damage.

Normal menstrual function depends on normal anterior pituitary function. Clauberg and Breipohl[289] confirm the claim of various preceding investigators that normal gonad function is determined by an

equilibrium between the hormones of the anterior pituitary and of the gonads. They showed by experiments that the anterior pituitary gland of castrated animals exhibits characteristic structural changes and contains a larger amount of gonadotropic hormones. Structure and hormone output become again normal under the administration of either follicular or corpus luteum hormones. In this connection must be mentioned a paper of Frank and Salmon[290] in which they demonstrate that the administration of follicular hormone (progynon B) leads to the disappearance of the gonadotropic factors of the anterior hypophyseal gland from blood and urine of women past the menopause. Excessive or prolonged estrin therapy, according to Emil Novak[230] actually inhibits the normal activity of the anterior pituitary which is so essential for the menstrual mechanism. "Since estrin does not influence ovulation, it obviously has no place in the treatment of sterility associated with amenorrhea." Sevringhaus[291] warns against the treatment of primary amenorrhea with ovarian preparations because larger doses will further inhibit the presumably already deficient activity of the anterior pituitary gland. However, literature is not wanting in reports of good results with ovarian extracts in amenorrhea.

Kaufmann[292] specifically stated that in cases of primary amenorrhea with underdeveloped uterus even large doses, approximately one million M. U. of progynon B, only rather exceptionally will result in a noticeable increase of the uterus. However, the experience of Janson,[293] using much larger doses, seemingly is quite different. In a twenty-one-year-old girl with a very small uterus and primary amenorrhea, the administration of a total of 26 million M. U. of progynon B led to gradual enlargement of the uterus until finally it had reached normal size. With cessation of the injections, there occurred one profuse hemorrhage lasting four days. Shortly afterward the woman married and became promptly pregnant. Kurzrok, Wilson, and Cassidy[294] mention that they obtained noteworthy results in primary and secondary amenorrheas with relatively large doses, around and above 100,000 R. U. of progynon B.

In the light of available information, estrogenic follicular extracts can be useful in the treatment of amenorrhea only in two possible ways: In large doses by stimulating growth of an underdeveloped uterus, and in small doses by possibly inducing improved activity of the anterior pituitary gland.

The purpose of every reasonable treatment of amenorrhea obviously is initiation of regular ovulations, which are dependent upon an adequate and well-balanced supply of the two gonadotropic hormones of the anterior pituitary. Most commonly, therefore, at present are employed the anterior pituitary-like hormones from the urine of pregnant women. Once more we shall quote in this connection Emil Novak:[230] Anterior pituitary-like substances are given because they show in animal experiments gonadotropic effects. For the human female, proportionately enormous quantities certainly would be required and even then we cannot justifiably expect a result, because the anterior pituitary-like substances used for this purpose are not produced by anterior pituitary glands but in the placenta. More will be said on this point later. Johnson[295] injected four monkeys daily with 200 R. U. of antuitrin-S (a pregnancy urine extract) to a total dosage of from 2,400 to 2,800 R. U. but failed to produce any histologic evidence of increased

luteinization in the follicles. Equally ineffective proved injections of antuitrin-S given to an immature animal over a period of two months to a total of 16,500 R. U. Rock and Bartlett[296] gave anterior pituitary-like extracts in moderate doses, intramuscularly, to a total of between 1,500 and 3,500 R. U. to amenorrheic women. Such doses failed to stimulate the ovaries sufficiently to cause any structural alterations of the endometrium.

We had already occasion to mention that Campbell[165] had no results with emmenin in the treatment of primary amenorrhea. Goldberg and Lisser[236] tried this preparation in 100 instances of menstrual disorders. It proved helpful in secondary amenorrheas of less than one year duration. They state that in practice the use of this substance of necessity will be extremely limited on account of its high price, which reminds one of a concluding remark made by Davidson[297] in a paper dealing with the use of estrin and progestin in the treatment of secondary amenorrhea: "Considering that a course of treatment, following the technic here described, costs about four guineas, and that to guarantee a result at least two courses are necessary, most probably three, it is obvious that this treatment can be administered only to a chosen few. Even then it is probable that only two or three periods will result in the majority of cases."

This offers an opportunity to emphasize that in the larger number of clinical reports the appearance of the first and probably only flow following organotherapy is considered sufficient to classify the result as satisfactory and, not so rarely, to count the case as "cured." However, Dunn[298] reporting results of hormonic induction of menstruation in 5 cases of amenorrhea of from three months to nine years duration (including one girl thirteen years old!) lays particular stress on the fact that by giving progynon B in daily doses of 90,000 R. U. to a total of 1,126,000 R. U. he was able to secure three consecutive flows after an amenorrhea of nine years in a woman forty-three years old.

Winter[298] finds from his experience that a secondary amenorrhea in a woman, who up to that time has menstruated regularly, rather calls for a thorough physical examination and most probably will not be cured by organotherapy. Practically the identical statement is made by Kaufmann.[232] He adds that if in such amenorrheic patients an endometrium capable of reaction is present, and if after administration of sufficiently large doses of follicular followed by corpus luteum hormones, a flow actually appears, only in about 25 per cent of the cases the cycles will continue spontaneously. Frank[21] reminds us that the majority of amenorrheas and menorrhagias are of a transient nature.

We have mentioned low-dosage irradiation of the pituitary gland and ovaries as a substitute for administration of anterior pituitary-like substances. A very detailed description of this form of x-ray therapy has been furnished by Wittenbourg and Porkhovnik.[299] Mazer and Spitz[239] qualify as a "stimulating dose" one only slightly larger than that employed in diagnostic procedures. Such a dose leads to an increase in cell activity without causing any histologic alterations discoverable in microscopic study. The stimulation of cell activity is due solely to biochemic factors. They warn that often repeated "stimulation" may cause "irritation" which may finally end in destruction of cells. "Restoration of ovarian function and of menstrual periodicity through low-dosage irradiation is evidence of true stimulation." The ovaries

are decidedly more sensitive to overirradiation than is the pituitary. Among others they give the following conclusions: About one-half of the 47 amenorrheic and 15 oligomenorrheic women were seemingly cured. The procedure proved in their hands definitely harmless. Stoeckl[300] refers to the commonly made claim, based on animal experiments, that these relatively small doses of x-ray could not possibly cause morphologic changes in the human hypophysis. He established the error of this claim. The death of a patient, thirty-eight days after administration of a total of only 610 r. to the pituitary region, gave him the opportunity to study the gland. He found about two-thirds of the anterior lobe necrosed. He mentions that in Vienna routinely only about 200 r. are given but that it would be impossible to deny that even this dose could cause histologic changes in the gland.

Merletti[301] claims to have cured many cases of amenorrhea by withdrawal of large quantities of blood by venesection. He feels that this method can well compete in effectiveness with organotherapy. He obtained particularly good results in amenorrhea due to psychic factors, which after all would not seem surprising.

In view of the previously mentioned rôle played by hyperactivity of the adrenal cortex in premature puberty, it was entirely logical for Neumann[302] to administer adrenal cortex extract to a woman suffering from Addison's disease, in whom the uterus had become atrophic and menstrual flows had stopped. He succeeded in restoring menstrual function.

Considering the present trend of using practically only hormone preparations in the attempt to restart menstruation, it seemed appropriate to Ripperger[303] to remind us that there have been employed in the past many useful emmenagogues for the same purpose. He carefully surveys the long list, now almost forgotten and discarded with the exception of a few at present still in use but solely as abortifacients.

We shall close with a reference to a recent, comprehensive paper by Tschertok[304] on the diagnosis and treatment of amenorrhea. Also he presents four graphic diagrams to show the interaction of various endocrines in relation to normal menstruation. He agrees with other writers that failures in hormone treatment often are due to insufficient analysis of type and cause of the condition in each individual case. He suggests the division of amenorrheas into the following 5 groups: (1) Changes in uterine mucosa with normal ovaries. In them there is no indication for hormone therapy. (2) Insufficient ovarian function with normal anterior pituitary activity. Administration of ovarian substances is indicated. (3) Insufficient anterior pituitary function. For this group he recommends alternating injections of anterior pituitary-like extracts and estrogenic substances. (4) Excessive activity of follicular apparatus. This cannot be influenced by hormone therapy. (5) Amenorrhea due to general causes. For them general hygienic-dietetic measures may be combined with organotherapy. His final conclusion is: Any schematic treatment for amenorrhea is useless and objectionable.

XIV. ANOMALIES OF INTERVALS AND OF MENSTRUAL BLOOD LOSS

This heading had to be selected for this chapter because there is at present no exact terminology available to express special forms of anomalies of interval or of amount of menstrual discharge. The term

opsomenorrhea (not mentioned in Stedman's medical dictionary, 13th edition) has been proposed for a menstruation in which the flows come periodically in long intervals. There can be no doubt that some individual instances of this condition in literature are recorded as "secondary" amenorrheas. We may state in this connection that, as far as we know, no claim has ever been made for any kind of therapy to be successful in changing a long interval menstruation into one of the typical four weeks type.

The term *oligomenorrhea* in gynecologic writings is indiscriminately employed to indicate either infrequent or scanty menstrual flows. (It is defined by Stedman as "scanty or infrequent menstruation," and by Dorland [17th edition] as "abnormally infrequent menstruation.")

The word *hypomenorrhea* has been suggested and is in use to specify regular but scanty flows. (It is rather vaguely described by Stedman as "deficient menstruation" and by Dorland as "a deficient amount of menstrual discharge.")

Polymenorrhea in both dictionaries is defined as "too frequent menstruation coming in shortened intervals."

We find the term *hypermenorrhea* used to express excessive blood loss due either to profuse or to protracted flows. It seems practically identical to the commonly employed term *menorrhagia* which implies a certain regularity of the flow as distinguished from *metrorrhagia,* which always indicates irregularity.

The promiscuous use of these not any too well definable terms in gynecologic literature makes it impossible to present here any clear picture of views held in regard to either etiology or treatment of the various types of menstrual anomalies affecting either interval, duration, or intensity of menstrual flows.

We have previously spoken of the factors generally assumed to account for regularity in menstrual function. There might be a qualitative or quantitative disturbance in the output of either the follicle-stimulating or of the luteinizing hormone of the anterior lobe of the pituitary, but more commonly a shortened interval is ascribed to the quicker involution of a presumably smaller corpus luteum, and long intervals to the opposite condition.

Abnormally large blood loss, leading to secondary anemia, requires gynecologic attention. The first task is to determine whether the free menstrual flow is caused by any local pelvic anomaly, especially one within the genital organs, or represents merely a functional disorder. Obviously we can deal in this review only with the latter.

Intervals, too long or too short, and flows too scanty, too profuse, or too protracted, are most commonly seen at the age of puberty, before the required harmonious interaction of the various endocrine glands associated in normal menstruation has been fully established, and at the preclimacteric age, when the established equilibrium becomes disturbed through senile involution of the ovaries. Rongy, Tamis and Gordon[305] write: Recent attempts to unravel the intricate mechanism of interglandular activity with particular reference to menstruation and its disorders have focused the attention of gynecologists on the functional disorders of the genital organs. It is now fairly well established that the disorders of menstruation in particular and of uterine bleeding in general may not have their origin in the genital tract but are often induced by an endocrine disturbance. It may be useful to quote here a

few historical facts enumerated by Campbell, Leudrum and Sevringhaus.[306] Hitschmann and Adler described the sequence of histologic changes in the endometrium, occurring during the menstrual cycle. When Kaufmann, Clauberg, and others were able to reproduce these changes by the administration of certain hormones, given in certain quantities and in a definite order, we were finally enabled to explain these morphologic changes in the terms of physiologic processes. Ample opportunity to study these changes in any given phase or even in all phases of one cycle was offered when methods were developed which made it possible to procure biopsy specimens with comparative ease and without noteworthy discomfort to the patient (by procedures which we have described previously in this review).

A specimen of endometrium procured at a known stage of the cycle permits certain conclusions in regard to the normal or disordered functional activity of the follicle or the corpus luteum. These points are made quite clear in a large series of microphotographs presented by Campbell and his coworkers. However, they feel forced to admit that it remains a fact that amenorrhea, cyclic follicular bleeding and menorrhagia of the endocrine type may be indistinguishable on the basis of endometrial histology.

For this reason the clinical course of the menstrual disorder and particularly certain hormone studies on blood and urine may be required for an exact diagnosis of the underlying cause. In regard to comparative studies of hormone levels in blood and urine, recent writers call attention to the possibility or fact that the transition of such hormones from blood to the urine necessarily depends on a certain renal threshold which possibly varies in the different phases of the cycle. It would be impossible to enter here in a discussion of this literature. We will give a quotation only from a paper of Schuschania[307] in which he speaks of the hormonologic and pathologic-anatomic pictures in cases of amenorrhea, metropathia hemorrhagica, and climacterium. In metropathia hemorrhagica, which undeniably is caused by an overproduction of follicular hormones, the follicular titer *in the urine* is below normal, probably because large quantities of the estrogenic substances are utilized in building up the hyperplastic endometrium. Siebke, just in these cases, has found high levels of estrogenic substances *in the circulating blood.* In cases of follicle persistence very little follicular hormone is present in the urine, while, on the other hand, large amounts of follicular hormone in the urine in cases of accelerated follicle ripening as a rule are seen associated with an atrophic and not with a hyperplastic endometrium.

An excess of follicular hormone thus can result in an hyperplastic endometrium which usually causes profuse or protracted menstrual flows but which at times entirely fails to pass through the secretory phase. This situation is described by Evans[40] as follows: Schroeder's disease, characterized by a hypertrophic endometrium and excessive bleeding, may be the result of a deficiency in gonadotropic hormones. Possibly only the luteinizing factor is deficient so that the effect of the other, the follicle-stimulating hormone, becomes relatively exaggerated. If under such conditions many follicles become cystic, they will actually pour out an excessive quantity of follicular, estrogenic hormone which will result in marked proliferation of the endometrium. In the absence of a sufficient supply of corpus luteum hormone, however, the result

will be a long-continued amenorrhea in spite of the hyperplastic endometrium. We must in this connection once more mention the already quoted paper of Stein and Leventhal[286] in which they explain an amenorrhea in association with small cystic degenerated ovaries in quite a different manner as due to mechanical interference with the ovulation process. While they advocate partial resection of ovaries for the cure of amenorrhea, Robinson[308] finds this same operation very useful for the cure of menorrhagia.

Burch and Burch[309] showed that menorrhagias not necessarily arise only from a "Swiss cheese pattern" endometrium. They found that biopsies repeated on the same woman not so rarely reveal in some cycles a mucosa without any glandular dilatations and again in other cycles a typically hyperplastic endometrium. "In the final analysis endometrial hyperplasia is a disorder of the hypophyso-ovarian equilibrium."

Undue prolongation of the menstrual flow, according to Hirsch-Hoffmann,[69] is the result of delay in the extrusion of the menstrual endometrium because of deficient or incomplete involution of the corpus luteum. Schroeder[3] dwells in detail on the relation of glandular cystic hypertrophy of the endometrium to disordered ovarian activity, a question also discussed by Tietze[310] and others.

Polycystic degeneration of the ovaries, in the belief of Kraul[311] represents the morphologic expression of the fact that the equilibrium in hormone production has become disturbed. Clinically this is manifested in fluor, sterility but chiefly in anomalies of the menstrual flow. Out of 100 patients with small cystic degenerated ovaries 48 had an oligomenorrhea (no amenorrhea is mentioned), 46 a polymenorrhea, and only in 6 was the menstrual function approximately normal.

We already had occasion to refer to the doubt of various writers in the rather common assumption that scantiness or entire absence of menstrual flows always indicates a deficient ovarian activity. Since amenorrhea, oligomenorrhea, and functional bleeding of any sort, writes Anspach[54] are unreliable as positive indices of ovarian function, a test curettage is important as a diagnostic aid.

Elden[312] emphasizes that there exists no definite relation of the particular type of menstrual disorder to any particular gland of the endocrine system. Haines and Mussey[313] discuss connections of amenorrhea, oligomenorrhea, and menorrhagia to a low basal metabolic rate in patients with thyroid hypofunction but free of any symptoms of myxedema. Their therapeutic results with thyroid preparations are noteworthy, and in the discussion of this paper Litzenberg fully supported their conclusions. Interruption of thyroid medication, in his experience, is usually followed by return of the previous menstrual disorder.

Systematic roentgenologic studies of the sella turcica convinced Bokelmann[314] not only of the value of this diagnostic method in judging sexual, functional disturbances in women, but as well forced him to the conclusion that in the interpretation of the various forms of hypogenitalism heretofore too much importance has been assigned to primary ovarian insufficiency. Practically identical are the conclusions of Fagioli[315] who emphasizes the frequency with which abnormally shaped and particularly large sellae turcicae are seen in women with disorders commonly ascribed to ovarian incompetence.

Haden and Singleton[316] found menorrhagias and metrorrhagias surprisingly common in women suffering from a simple achlorhydric, hypo-

chromic anemia, which in literature also appears as chronic chlorosis or chlorotic anemia with achlorhydria. The disease responds almost specifically to iron therapy. With return of the blood picture to normal, the menstrual disturbance usually disappears promptly. Kuestner,[185] as already mentioned, believes that general endocrine activity and with it menstruation can become impaired by frequent or continued overexposure to ultraviolet rays during sport activities. However, erythema doses of ultraviolet rays over the lower abdomen, diathermy, and simple heat applications, in the belief of Gillerson, Warschawer and Tykotschinskaja[316a] are particularly useful because they stimulate the vegetative nervous system. Disturbances of the latter account for endocrine disorders which unfavorably affect the menstrual function. Infrared rays, on the other hand, according to Amstel[317] exert a most beneficial influence both on growth and sex hormones and for this reason are of great service in the treatment of amenorrhea, menorrhagia, vulvitis, pruritus, and krausosis vulvae. Lehmann[318] offers an exhaustive and critical analysis of the efficacy, in the treatment of ovarian insufficiency, of such physiotherapeutic methods as application of ultrared or ultraviolet rays, galvanic and high frequency currents, diathermy, short waves, massage, radium and x-rays. A paper of Francillon-Lobre[319] deals specifically with short wave therapy. In a large percentage of his cases, these waves resulted in disappearance of such disorders as amenorrhea, oligomenorrhea, and menopausal difficulties and incidentally also improved, as a rule, the patient's general health. In a statistical, clinical, experimental and therapeutic study of the effects of the seasons and of light on genital function, Kirchhoff[320] arrives at the following conclusions: Exhaustive investigations of this cosmobiologic problem permit the deduction that light within certain wave-lengths definitely influences sexual hormonic processes. This finding has practical significance so far as red light is concerned, which benefits markedly all hypohormonal disorders of women.

A method, years ago first recommended by German gynecologists, namely roentgenization of the spleen, in the experience of Vignali[321] proves particularly useful in the treatment of pubertal hemorrhages. Dogliotti[322] advocates for this same purpose repeated, small (10 c.c.) transfusions of blood. Holzapfel[323] resurrects another old German therapeutic method known as athmocausis, consisting in the partial destruction of the endometrium by means of steam in cases of menorrhagia. Discussion of intrauterine application of radium for this purpose we leave for a later chapter.

Newer ergot preparations are extensively used for reducing menstrual blood loss. Among these, gynergen seemingly is enjoying particular popularity, and it, therefore, may be useful to mention a few reports of disagreeable by-effects of this preparation. Balcke[324] saw gangrene of an extremity follow its use. The same accident is recorded by Cahill,[325] and his report was promptly followed by one from Gould, Price, and Ginsberg[326] who quote other such cases from the literature.

XV. MENOPAUSE

In the introductory remarks of a comprehensive survey of the symptoms and treatment of the menopause, Mazer and Israel[327] point to the fact that generically the term "menopause" implies the physiologic cessation of the menstrual function. Actually menopause marks the

completion of the "climacteric" period of transition which is characterized by varied manifestations of the pluriglandular reactions to the decline of ovarian function. In spite of this difference, the terms "menopause" and "climacterium" are usually employed synonymously. Therefore, among the symptoms of the menopause, outside of cessation of menstrual activity, commonly are included irregularity of flows, disturbances in the function of pituitary, thyroid, adrenal, and other glands, usually associated with a marked instability of the autonomic and particularly vasomotor system.

It seems that not sufficient emphasis is placed on the noteworthy fact that with normal, senile involution of ovarian activity the common general molimina often appear long before final cessation of menstrual flows, while in cases of operative or radiation castration usually some time elapses before these symptoms manifest themselves. An explanation for this difference may be found in the fact that in case of normal involution the balance between folliculin and progestin becomes gradually disturbed, while in artificial castration, certainly with removal of the ovaries both hormones are eliminated simultaneously. Women suffering from severe symptoms after natural climacterium often show large amounts of estrogenic substance in the urine. More recently also differences in the urinary levels of the two anterior pituitary-like hormones have been connected with certain symptoms, but views in this respect are not yet clearly enough defined to be quoted here. We know that partial or complete loss of ovarian function (Evans[40]) leads to excretion of increased amounts of gonadotropic hormones in the urine, associated with morphologic changes in the pituitary gland, which can be reversed to normal (Clauberg and Breipohl[289]) by administration of either of the two ovarian hormones.

In contradiction to other investigators, Westman[328] maintains that reactivation or rejuvenation of ovaries by means of gonadotropic hormones is possible. In two women, respectively fifty-one and forty-eight years old, both having passed through their menopause, he transfused intravenously, one week before required laparotomy, 225 and 400 c.c., respectively, of blood taken from pregnant patients near term. In the first woman, he found a follicular vesicle with partial luteinization of the granulosa cell membrane surrounded by small hemorrhages. In the other, there were present follicular vesicles in both ovaries with a markedly hyperemic granulosa membrane. Similarly Heimann,[329] in experiments on guinea pigs, found that ovaries severely damaged with x-rays can be completely restored with administration of anterior pituitary hormones.

In regard to certain anomalies observed during the menopause, we will mention Maranon's[330] assertion that hyperthyroidism, often evident in climacteric women, rarely is found associated with struma or exophthalmus. In the belief of Goldberg[331] acroparesthesia, a very common complaint of women in the menopause, has so far not been sufficiently investigated. He records good results with ovarian preparations. Pisk[332] finds that the various forms of neuralgia which develop during the menopause and often prove refractory to the usual antineuralgic treatment, may respond well to follicular hormone which he administers in daily doses of 200 M. U. Curschmann[116] described two cases of climacteric edema. It is transient and possibly not rare, though it is presumably often erroneously ascribed to a cardiac or renal anomaly. For this

reason alone, he emphasizes, it is of great clinical importance to know that a typical edema of menopause exists. In one of the cases the edema disappeared promptly and permanently with the use of progynon.

A specific hypertension of the climacteric woman is denied by many authors. Such women obviously are at an age when arterial and nephritic disturbances are relatively common. Different views have been expressed lately. Crainicianu and Jonesco[333] claim climacteric hypertension to be a specific morbid entity, the result of predisposing factors (age, arteriosclerosis, and disturbed endocrine function) to which finally is added hyperactivity of the adrenal cortex due to elimination of ovarian function which normally acts as an inhibitor on the adrenals. In about one-half of such patients, they succeeded in lowering the high blood pressure by intravenous administration of folliculin. Schaefer[334] reports substantial reduction of hypertension and amelioration of all accompanying symptoms with theelin in 13 menopausal women. But, on the other hand, we find Langeron[335] contending that hypertension during the menopause is not necessarily caused by the latter, since in 21 per cent of such cases he could establish definitely other causes for the increased pressure. He found ovarian therapy of very little use in this condition. That this particular question cannot be considered as settled can easily be seen from a paper of Steinkamm and Giesen.[336] In 35 women one intravenous injection of 200 M. U. of progynon almost typically lowered the blood pressure; a maximal depression of 25 mm. Hg was seen in menopausal women with marked vasomotor disturbances. However, using another 35 women as controls, they were able to ascertain that the identical effect can be obtained by making an intravenous injection of normal saline injection. In their own experience intramuscular injections of follicle hormone, even in large doses, never influenced an hypertension.

Emil Novak[230] admits that we possess no definite information concerning the causation and nature of those curious phenomena of menopausal women, though they evidently are of vasomotor origin. Empirically we know that they follow elimination of ovarian activity and often are most troublesome when ovarian function apparently becomes deficient. Since complete cessation of ovarian function always induces hyperactivity of the anterior lobe of the hypophysis it seems plausible to ascribe the vasomotor disturbances to an excess of anterior pituitary hormones. Therefore, it seems logical to attempt an inhibition of anterior pituitary overactivity, at least in the premenopausal state, by means of estrogen substance.

Approximately on this basis, Collins, Thomas and Menville[337] justify their recommendation of inhibiting anterior pituitary function by a large, inhibiting dose of x-rays directed toward the gland. They believe that such a dose has a destructive effect, thus prevents further production of prolan. Histologic and hormonologic proof for such an effect, however, is still wanting. (See report on destructive effect of smaller doses by Stoeckl.[300]) Similar ideas are expressed by Asaturov[338] who relieved partially or completely 27 menopausal women of all their discomforts by roentgenization of the hypophyseal region. According to Huet[339] good effects occur even with dosages as low as 2,000 r. though usually 3,000 r. are required, given in 6 sittings, 500 r. each, applied through three fields.

It seems superfluous to discuss here in detail the large and mostly controversial literature dealing with the relative values or advantages of roentgenization of but one ovary, hysterectomy, or intrauterine application of radium in the treatment of functional hemorrhages. The decision in each case must be made with consideration of many individual features as is so well shown in a paper of Keene and Payne.[340]

Experimenting on guinea pigs, Loeser[341] found that removal of the ovaries stimulates the output of the thyrotropic hormone of the anterior pituitary gland. In his belief, his good results in ameliorating the hyperthyroid symptoms of menopausal women with di-iodotyrosine are due to the fact that this drug reduces secretion of the thyrotropic hormone by the hypophyseal gland.

Fumarola[342] considers a belief in a specific climacteric neurosis unjustified. In most instances such a neurosis is only an incidental complication of the menopause. The few cases of seemingly true climacteric neurosis are really only particular forms of neurasthenia with exaggeration of vasomotor symptoms. But this form is characterized by its resistance to all forms of treatment and usually is only partially controlled by organotherapy.

Whittingdale[343] justly stresses the necessity of a most careful examination, because many other coincident conditions or diseases can produce most confusing symptoms. He divides these patients roughly into two groups: the fat women, often with symptoms of arthritis, who must be reduced by diet and occasionally with thyroid, and the thin ones, who more often complain of insomnia, flushes, eructations, heart palpitation, etc. They usually require bromides, valerian, and other sedatives as well as a high caloric diet.

Bauer[344] contributes a paper dealing specifically with the dietetic treatment of menopausal molimina. In general there is required restriction in proteins together with lessened physical activity. In instances of hypertension, a long-continued reduction of salt intake is important, often to be combined with reduction of protein intake. In stout individuals with hypercholesteremia, which is almost the rule in the combination of obesity with hypertension, all fats rich in lipoids must be avoided. In climacteric women with arthritic symptoms any excess of salt intake must be avoided. Hot flushes can be momentarily relieved by cold drinks, especially of effervescent waters. Crainicianu[345] extols the value of calcium lactate which improves the tonus of sympatheticus and vagus. He claims 86 per cent cures, 12 per cent improvement, and only 2 per cent failures in the treatment of all menopausal symptoms due to ovarian insufficiency. Bakaćs[346] finds calcium in combination with parathyroid most effective in controlling profuse flows; McFarlane[347] finds emmenine useful for the relief of menopausal molimina.

In the belief of Aschner,[348] the therapeutic results of gynecologic specialists in dealing with the menopausal woman are so unsatisfactory, because at this stage of life women are prone to develop anomalies which fall into almost every field of pathology. For this age, specialists in all branches of medicine record a higher incidence of glaucoma, cataract, iritis, scleritis, herpes, pruritus, eczema, arthritis, cardiac and renal disorders, neuralgias, emotional disturbances, etc. Naturally the symptoms of any of these diseases may be intensified or distorted in the presence of true menopausal molimina. Aschner agrees with Wiesel's contention that prevailing theories concerning the origin of these

molimina, representing a combination of physiologic and pathologic phenomena, are unsatisfactory. These theories are not generally applicable, because the clinical picture in the individual case is always determined by certain constitutional factors. Therefore, Aschner,[130] in another paper, concludes that constitutional and not specific therapy offers the best chances, especially when dealing with neuroses or psychoses.

Also Sevringhaus[291] refers to the fact that climacteric disturbances often include periods of autonomic, emotional, and psychic instability which may last anywhere from a few days to nearly two decades in some instances. Hence, he reminds us, it always is difficult to make any statement that any particular therapy alters the duration of any symptoms, and especially so because there is never any control series available for the scientifically desirable test.

It seems appropriate to mention in this connection a paper read by Schneider.[349] In it he reported excellent results obtained with estrogenic substances in the treatment of dysmenorrhea, secondary amenorrhea, menorrhagia, metrorrhagia, and sterility. In discussing this paper, Jean Paul Pratt recalled his very fine results reported ten years ago with small doses of follicular substance. With careful recheck later he was forced to the conclusion that they actually were most disappointing. At present he injects into patients referred to his department in the hospital for severe menopausal symptoms either a preparation of theelin in oil or the same kind of oil without any theelin. Just as much improvement has followed the one kind of injections as the other kind, though the results are not judged by him but by the referring physician who does not know whether the patient received theelin or simply pure oil.

This discussion of the medicinal treatment of climacteric discomfort we may well end with a reference to a fact known to all experienced practitioners: For the majority of worried, frightened, and emotionally disturbed women, premenopausal or postmenopausal, a quiet, encouraging, and occasionally reiterated explanation of the situation proves the most helpful and effective sedative.

The methods of possible prevention of disagreeable menopausal discomfort apply in general to operative measures.

Preservation of some ovarian tissue in the course of radical operations when necessary in relatively younger women is common practice. Unfavorable aftereffects of this conservatism, of course, are known.

Transplantation of ovarian tissue into other parts of the body is an old practice. Moure,[350] using the method of Donay, transplants one ovary into one of the large labia. In discussing the favorable effect in his cases, he duly appreciates the merely psychic influence on the patients who are thus enabled to ascertain by palpation the presence of an ovary and to observe its functional activity by noticeable changes in its size. He feels that results could be greatly improved by an added transplantation of endometrial tissue into the cervical canal, so that also the bleeding phenomenon would be preserved. Transplantation of endometrial tissue into the cervix proved successful in preventing menopausal molimina in 8 cases reported by Fuchs.[351]

Quite recently Solomons[352] described a case in which not only an ovary but also a piece of functionating endometrium was successfully transplanted from one woman to another. After years of amenorrhea

this woman again began to flow regularly. Stanca[353] found that the maximal duration of life of an autotransplanted ovary in 120 cases amounted to thirty-nine months. Tonkes[354] arrived at the conclusion that there is little sense these days to transplant an ovary in a case of supravaginal hysterectomy without simultaneous transplantation of endometrium. It seems that a functionating endometrium always preserves the ovary against degeneration.

In conclusion, we shall cite the ingenious operation devised by Strassmann[85] for overcoming amenorrhea in women in whom the uterine cavity for one reason or another has become atretic or obliterated, but who still possess functionating ovaries. Splitting the anterior uterine wall, he forms a channel into which he draws and sutures one tube. In 6 patients so operated upon, regular flows started and menopausal symptoms disappeared promptly. Somewhat optimistically, or humorously, Strassmann adds: "So far no pregnancy has been recorded." He speaks of this operation as a method of restoration of a functionating menstrual channel. Inevitably some discussion started among German writers whether these subsequent periodic flows can be justifiably called "menstruation" since they do not represent bleeding from an endometrium in its secretory phase. Correctly termed, they are pseudomenstrual vicarious flows from the tubal mucosa.

XVI. SEXUAL HORMONES AND ORGANOTHERAPY

In the preceding chapters at the appropriate occasions mention has been made of the various hormone preparations now in common use. It seems, however, desirable to offer furthermore a brief survey of papers which deal rather with the general aspect of sexual hormonology and organotherapy.

Nielsen[355] thinks that a revision of all theories concerning origin and activity of sexual hormones becomes necessary. Analyzing the chemical formulas of the various sex hormones, he shows that not only the male and female sex hormones but also the vitamins and cholesterin are built upon the carbohydrate radical $C_{17}H_{28}$. He concludes that there are not only three so-called sexual hormones but a whole series of substances, all closely related to each other, which without exceptions exert a stronger or weaker biologic effect. They are sterines, present in all organs, and any conception of specificity or of solely ovarian origin, e.g. of estrin, must be discarded. Estrin is present in large quantities in the urine of the male horse and is found in small amounts in the urine of human male. Only in analogy to known facts in regard to thyroxin, insulin, or adrenalin, the erroneous conclusion has been made that estrin is the product of the ovaries and androsterone that of the testicle. It would seem more logical to regard the sexual hormones solely as links in the chain of sterine metabolism.

Very similar are the views expressed by Windaus.[356] He proves the close chemic connection between all these substances and shows that both male and female sex hormones fall into the chain of derivatives of cyclo-pentano-perhydro-phenatren. Seguy[357] who reviews all available proofs that the characteristic follicular hormone certainly is not produced in the ovaries alone but is found in many other active cell tissues as a derivate of sterines, deals with this same question. Goldhammer and Loewe[358] examined the urine of 64 men between the ages of nineteen and fifty-one years. In 32 perfectly normal men, the urine

of only 19 per cent gave a positive reaction for follicular hormone. In 32 other men, with certain anomalies of the vegetative nervous system, especially in regard to sexual function, this reaction was positive in 65.5 per cent.

In a very interesting paper, Seitz[359] recently discussed the follicle hormone as a specific growth hormone, which during pregnancy, as a matter of fact, is produced by the chorionic tissue in large amounts together with anterior pituitary-like hormones and probably also a substance biologically identical with the corpus luteum hormone. Ehrhardt[360] confirms previous findings that both the young and the ripe placenta contain corpus luteum hormone, seemingly in varying amounts.

Allen[7] thinks that the close relation of chemical structures of follicular and luteal hormones, secreted by the same cells in different phases, suggests the possibility that progestin may be formed by a change in the molecule of the estrogenic hormone. In the opinion of Marshall,[361] the reproductive hormones are metabolic by-products before they acquire hormonic activities.

Nielsen, in his aforementioned paper, stated that only, when by means of artificial synthesis sufficient quantities of these various sterine derivates will become available, we shall be enabled to make exact studies concerning their respective biologic effects, an essential desideratum for their intelligent administration in therapy. It seems that this goal has almost been reached.

Progesterone, the crystalline hormone of the corpus luteum, has been synthesized from stigmasterol, closely related to cholesterol, and from cholesterine by Tavaststyerna.[362] Theelin in crystalline form has been produced from ergosterol, a plant sterol. Androsterone has been manufactured from cholesterol. Viosterol is obtained by irradiation of ergosterol with ultraviolet light.

Summarizing available information concerning the chemical structure of all these various substances, Ruzicka[363] concludes that all of the sexual hormones can be considered as derived from cholesterol. They all contain a nucleus consisting of four carbon rings. The sex hormones differ from each other only in the side-chain arrangements around the common central nucleus.

Butenandt[364] described the synthetic production of a presumably pure corpus luteum hormone either from stigmasterine (the sterine of the Soya bean) or from sterines extracted from the urine of pregnant women. Kaufmann[13] tested the substance synthesized from stigmasterine on castrated women after having first produced endometrial proliferation by means of 300,000 M. U. of progynon. Six milligrams of this substance given daily for five days resulted in a menstruation-like flow. Biopsy showed the endometrium to be in the typical secretory phase. In Kaufmann's belief this experiment definitely proves that this chemical product is physiologically equivalent to the corpus luteum hormone.

Preissecker[365] points out that a ready supply of corpus luteum preparation, at least theoretically, could be most useful: (1) In the production of pseudomenstrual flows in women without active ovaries; (2) in the prevention of certain types of abortion; (3) in amelioration of pain due to uterine spasticity (dysmenorrhea); (4) in the initiation of menstruation in cases of primary and secondary amenorrhea (after preceding stimulation with follicular hormone); (5) in influencing the duration of, and interval between, menstrual flows; (6) in correcting

climacteric disturbances, including menorrhagia; (7) in the cure of intermenstrual pain and bleeding; and (8) in the treatment of sterility.

Runge[366] dwells on the possible importance of synthetic progesterone and particularly vitamins in the organotherapeutic armamentarium of the gynecologist.

Synthesized estrogen and progesterone, available in sufficient quantities and presumably then at a lower cost, will obviously limit present efforts of stimulating the production of these hormones in the patient's ovaries either by administration of gonadotropic, anterior pituitary-like substances or by irradiation of the pituitary gland for the purpose of increasing its output of gonadotropic hormones.

We had previously occasion to point out that the gonadotropic substances extracted from the urine of pregnant women in their biologic effects on testicles and ovaries are not identical with the gonadotropic hormones secreted by the anterior lobe of the pituitary (Schockaert[367]). Siegmund[368] suggests that the effect of anterior pituitary-like substances on the ovary depends upon the maturation stage of the follicle. Primordial follicles, even in adult individuals, do not react at all. Follicles of juvenile ovaries, when they contain a small amount of fluid, react the more promptly the further maturation has progressed. We also have referred in a preceding chapter to the theory that anterior pituitary-like hormones prove effective on the ovaries only when their influence "synergistically" is strengthened by substances simultaneously supplied by the hypophyseal gland. This view is not fully shared by Zondek.[5]

Accurate evaluation of clinical results with endocrine products as reported in the literature is practically impossible at the present state of wide discrepancies in standardization and in view of the failure of many writers to indicate dosage at least in specific unit terms. Thus in regard to the corpus luteum hormone, Corner[10] states that the Clauberg unit represents about one-half of the potency of the Corner-Allen unit, though it is often asserted that it amounts to only one-fifth. In regard to standardization of estrogen-producing substances, a final solution has not yet been reached. Lacqueur[369] emphasizes the difficulties caused by the fact that reactions differ in different animals of the same species. He, therefore, suggests that all comparisons of strength be made solely with the preparations supplied by the Standardization Committee of the League of Nations. Schoeller, Dohrn, and Hohlweg[370] consider even this procedure too inaccurate. Bourg[371] proposes an entirely new method of determining potency by testing the preparation in regard to its effect on the growth of the uterus of castrated rabbits. Coggi[372] recommends the use of the benzoate of folliculin which in animals shows an effect 30 per cent greater than that of the usual folliculin, and also in the human being gives better results. Its main advantage, however, is the possibility of determining exactly the required dosage by weight.

An Editorial in the London Lancet (2: 295, 1936) stressed the evident fact that sex hormone therapy could be put on a scientific basis only by general adoption of units of international validity. "It is quite impossible to compare accurately amounts expressed in mouse, rat, or rabbit units in published investigations from different laboratories or clinics."

Obviously therapeutic effects of the same preparation will differ under varying modes of administration. Only a small number of the marketed preparations, writes Biskind,[373] are known to contain active material. Of the latter only very few, among them the estrogenic principle, are effective when administered by mouth. There is no satisfactory evidence that any of the pituitary preparations can be successfully given orally.

Only pure hormone products, stable and free of all toxic by-products, should be employed for subcutaneous injections. In this form they are decidedly more potent.

Urine of pregnant women has been used in form of enemas. Tachezy[374] and Warschawsky,[375] as well as Siegert, consider such rectal administration unesthetic but convenient, cheap, and useful. All the advocates of this form of application realize that such urine contains outside of anterior pituitary-like substances also other hormones and possibly toxic material. Some endocrinologists have and still employ (of course, without knowledge of the patient) disguised urine for oral use.

In relation to percutaneous administration, we must mention the claim of Vogt[376] that applications of mud and mud baths are effective on account of the hormone contents of mud. We have previously spoken of application of anterior pituitary-like substances in form of salves by inunctions as recommended by Koschade.[240] Zondek[377] is convinced that the estrogenic principles are effective in oral, rectal, subcutaneous, and percutaneous administration. The last mentioned exhibits definite local effect, and for this reason is particularly valuable in the treatment of certain forms of pruritus vulvae or acne. He does not refer to local use in cases of senile vaginitis, but it would seem logical to make experiments in this respect.

Unique is Stanca's[378] administration of ovarian extract by means of direct injection into the ovary. In a nineteen-year-old girl with primary amenorrhea, suffering from very frequent epileptic attacks, he injected during a required laparotomy 1 c.c. of ovarian extract into each ovary. Within twelve days the first menstrual flow appeared. After three more flows the patient became pregnant. When seen two and one-half years later, the patient was still menstruating regularly and had had no epileptic attack since operation. Stanca feels that intraovarian injection of folliculin may have its own specific effect.

Much interest has been shown in the immediate fate of therapeutically administered hormone substances. According to Silberstein, Molnar and Engle,[379] injected follicular hormone, in experiments on dogs, was rendered inactive within two hours by the circulating blood and the liver. Studies made by Robson, Mac Gregor and others[380] indicate that the human body rapidly destroys, makes inactive or eliminates administered estrogenic hormone. For instance, four hours after injection of 10,000 M. U. the blood contained less than 25 M. U. per liter. Zondek's[381] findings were as follows: After oral or subcutaneous administration of folliculin (hormone) only very small amounts can be recovered in active form from the urine. A woman, forty-five years old, receiving over 500,000 M. U. eliminated in the urine only 3 per cent. That the administered hormone becomes inactivated within the body, in his belief, is proved by the fact that it can be reactivated by hydrolysis. The inactivation seemingly takes place in the liver under the influence of ferments; however, the benzoate form of the ovarian hormone is not inactivated in this manner.

Rather conflicting views are expressed concerning undesirable and unexpected by-effects of potent hormone preparations when administered either in large doses or for a long time. Bachman, Collip, and Selye[382] reported that in adult rats daily injections of anterior pituitary-like substances, when continued for long periods, resulted in the production of a definitely antigonadotropic substance in the blood. Emil Novak[230] speaks of this finding as the "bedeviling concept of an antihormone" developing under continued hormone introduction, and hopes that it will not be found true for theelin. He must have felt pleased to see the assertion of D'Amour, Dumont, and Gustavson[383] that their investigation failed to ascertain the formation of antihormones under administration of estrin. They suggest that Collip's antihormone possibly is only an antibody developed under the effect of protein substances contained in the injected preparations.

More or less emphatic warnings against reckless use of potent hormone products mostly refer to follicular substances. This possibly is due to the fact that the estrogenic principle among all sex hormones was the first to become available in high concentration and thus is the one in greatest and longest use.

Any direct harmful effect of theelin or similar preparations on the ovaries is denied by Allen and Diddle,[384] Buschbeck[235] and others, which is not surprising since, as a rule, an endocrine gland is not affected by its own hormone extract. Nevertheless we find Mazer, Meranze, and Israel[385] making the following statement: Doses relatively much larger than those employed clinically did not produce macroscopic or microscopic changes in any of the vital organs of rabbits. The response of the ovaries to very large doses is either degenerative or stimulating, dependent upon species and age of the animals and upon the duration of administration.

Estrogen administration certainly affects pituitary function and thus indirectly ovarian activity. Without going here into details or repeating what already has been said in this respect in preceding chapters, we shall quote but a few authors. Clauberg and Breipohl[289] definitely showed that continued large doses of follicular hormone suppress the output of gonadotropic hormones by the hypophysis and that this function is restored to its previous level immediately after cessation of further administration of folliculin. Observations made by Frank and Salmon[290] established that progynon B causes prompt reduction and within twenty-eight to eighty days complete disappearance of the anterior pituitary-like substances in the urine of menopausal women. Discontinuation of progynon at once is followed by reappearance of these substances in the urine. Identical findings are reported by Jones and Mac Gregor[386] who experimented on 10 women at ages between fifty-two and eighty-three years. Noteworthy to the clinician, however, would seem the fact that in 7 of these 10 old women uterine bleeding started. Mazer and others,[385] in a clinical study, ascertained that a total of 100,000 to 200,000 R.U. of estrogenic substance, given to patients in divided doses over periods of two to three months, produced no appreciable changes in body weight, basal metabolism, blood pressure, blood counts, coagulation and bleeding time, blood chemistry and urine. However, in 6 out of 17 regularly menstruating women such large quantities of follicular hormone produced delay of menstrual flows from one to three weeks "apparently as result of an inhibitory effect on the anterior lobe of the pituitary."

Very important information concerning this functional impairment of the hypophysis has recently been furnished by Zondek.[387] Injections of folliculin can reactivate the ovaries of a senile mouse, so that estrus again will occur regularly. This fact can be explained only by restoration of discontinued or weakened gonadotropic function of the anterior pituitary lobe. Other experiments were made by Zondek on rats and chickens to ascertain the effect of continued administration of follicular hormone in moderate doses. Prolonged administration definitely interferes with anterior pituitary function, but this effect does not manifest itself either equally or simultaneously on all the various hypophyseal hormones. The output of the gonadotropic principles seems most sensitive and therefore atrophy of the genitalia in rats appears as the first result. The ovaries become so small that they cannot be identified with the naked eye. They may contain a few, very small follicles but never corpora lutea. The effect on birds seems to be identical. Next affected is the growth hormone. Pituitary gland and adrenals, however, become enlarged. If the follicular treatment is discontinued after several months, the animals do not spontaneously resume growth, which however promptly starts with administration of Evans' pituitary growth hormone. Zondek gained the impression that administration of follicular hormones actually stimulates the production of other hypophyseal hormones, e.g. the thyrotropic and parathyrotropic.

In similar experiments on 10 old women, Jones and Mac Gregor[386] found that estrogenic substances do not inhibit production of the diabetogenic hormone of the anterior pituitary lobe.

Not so rarely writers mention marked increase in libido as undesirable by-effect of folliculin treatment. Obviously this effect is particularly inconvenient in young children and old women. Since the introduction of theelin by Lewis[388] for the treatment of gonorrhea in children, authors repeatedly have referred to enlargement, at times painful, of the breasts, slight bloody discharges or aroused libido as occasional drawbacks in this therapy.

Zuckermann and Morse[389] assert that large doses of estrin can lead to excessive hyperplasia of the endometrium with extensive necrosis of the superficial layers and cyst formation in the deeper layers.

It would lead us too far to quote literature discussing the rôle possibly played by excess amounts of estrogen in structural changes of the cervix suggesting malignancy or in the etiology of myomatosis or endometriosis. Cesa[390] describes such intense changes in the cervix following large doses or prolonged administration of estrogenic material. Incidentally he also asserts that these alterations again disappear under the influence of corpus luteum hormone.

On better evidence rests a belief in possibly harmful effects of excessive doses of folliculin on the breasts. We have already spoken of the studies of Taylor[135] concerning the relation of chronic mastitis to certain hormones of the ovary and pituitary. Mac Donald,[391] on the basis of experimental investigations, denies that either estrin or progestin could produce specific pathologic lesions such as cystic disease or adenosis of the mammary glands. However, very recently, Herold and Effkemann[392] came to opposite conclusions. They found that administration of follicular hormone for only a limited time, in adult female rats, results in the appearance of cyst formations arising from either acini or milk ducts. In their opinion, this effect is very similar, if not identical, to the glandular cystic hypertrophy of the endometrium so

characteristic for an increased supply of follicular hormone. Other investigations made by them, in their belief, strongly suggest that in the genesis of fibrosis mammae cystica of women a continuous excess of this hormone plays a significant part.

At the 1936 meeting of the American Gynecological Society, Emge expressed justifiable doubt whether it is safe to administer large doses of potent hormonal substances over long periods of time without the possible risk of awakening to activity dormant carcinomorphic elements. In a recent meeting of German gynecologists one speaker, referring to the striking chemical similarity of hormonic to carcinogenic substances, warned that indiscriminate use of such preparations at the present state of our information might well be contrary to the principle, sacred to every physician "*Nihil nocere.*"

Some justification for extreme caution can be found in the possibility, if not likelihood, of damage to germ plasm as the result of endocrine therapy. Wolff[393] has definitely established such permanent damage for the white mouse. Therapeutic administration of prolan can lead to the production of defective ova as result of precipitated follicle maturation. Quite recently (in 1937) Wolff published further observations made on the human female, and concluded that prolan should not be given to women still in the childbearing age and particularly not in cases of amenorrhea when anterior pituitary-like substances often are used in large doses in the attempt to induce ovulation for the purpose of restoring fertility.

We will simply list a few of the authors who estimate in comprehensive form the value of marketed preparations for the treatment of the various disorders of the menstrual function: Benthin,[279] Biskind,[373] Frank,[21] Kaufmann,[232] Meigs,[241] Neumann,[394] Emil Novak,[230] and Josef Novak,[281] this last mentioned writer concluding his summary with the statement: "Very much is still in complete darkness. Within the next few years, however, we probably shall learn many new facts and will have to forget much of the present." Many others of these summaries sound not any less skeptic.

In conclusion, it seems well worth while to repeat a few of the comments made in an Editorial of the Journal of the American Medical Association of Oct. 24, 1936:

In order not to be outdone by a colleague, physicians demand the hormones (from the manufacturers) as rapidly as they can be separated from the tissues, blood, or excreta of animals or man, and proceed to inject them into patients.

A disturbing feature is that the medical literature is being filled with articles which are almost unanimously enthusiastic and which often give evidence of lack of critical consideration.

It is difficult to find articles recording failures. One never sees in print, e.g. a report of an experience like that of an endocrinologist who injected an extract into a fifteen-year-old girl for dysmenorrhea. The size of the ovaries seemed normal before the injections were given. At the conclusion of the treatment, an acute appendicitis developed and at operation the surgeon found bilateral cystic ovaries the size of oranges.

For the present only those clinicians with facilities for critical study should be encouraged to administer the newer endocrine preparations to patients, and these clinicians should be urged to publish their negative results as well as their positive results.

A large group of physicians should cease their indiscriminate injections of unknown substances into unsuspecting patients.

REFERENCES

(257) Human Biol. **6**: 431, 1934. (258) Orig. in Japanese. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **28**: 110, 1934. (259) Orig. in Japanese. Abst. in Ibid. **32**: 542, 1936. (260) Orig. in Japanese. Abst. in Ibid. **27**: 632, 1934. (261) China M. J. **48**: 642, 1934. (262) Orig. in Polish. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **26**: 86, 1934. (263) Arch. f. Gynäk. **159**: 12, 1935. (264) Orig. in Russian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **29**: 522, 1935. (265) J. Obst. & Gynaec. Brit. Emp. **40**: 792, 1933. (266) Zentralbl. f. Gynäk. **57**: 2897, 1933. (267) Med. Klin. **32**: 17, 1936. (268) Orig. in Italian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **23**: 597, 1933. (269) Zentralbl. f. Gynäk. **60**: 728, 1936. (270) Zentralbl. f. Gynäk. **60**: 3016, 1936. (271) Schweiz. med. Wchnschr. **63**: 585, 1933. (272) Zentralbl. f. Gynäk. **61**: 399, 1936. (273) Ztschr. f. Morphol. u. Anthropol. **33**: 43, 1935. (274) Arch. f. Kinderh. **103**: 97, 1934. (275) Ztschr. f. d. ges. Neurol. u. Psychiat. **146**: 548, 1933. (276) Am. J. Obst. & Gynec. **31**: 213, 1936. (277) Ibid. **28**: 596, 1934. (278) Ibid. **32**: 495, 1936. (278a) Arch. f. Gynäk. **151**: 400, 1934.

(279) Med. Klin. **31**: 233, 1935. (280) Am. J. Surg. **33**: 345, 1936. (281) Wien. klin. Wchnschr. **49**: 337, 1936. (282) Orig. in Italian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **25**: 299, 1933. (283) München. med. Wchnschr. **83**: 1722, 1936. (284) Zentralbl. f. Gynäk. **60**: 2711, 1936. (285) Ibid. **59**: 2945, 1935. (286) Am. J. Obst. & Gynec. **29**: 181, 1935. (287) J. A. M. A. **107**: 1286, 1936. (288) Am. J. Obst. & Gynec. **31**: 14, 1936. (289) Arch. f. Gynäk. **158**: 567, 1934. (290) Proc. Soc. Exper. Biol. & Med. **33**: 311, 1935. (291) J. A. M. A. **104**: 624, 1935. (292) Klin. Wchnschr. **12**: 1557, 1933. (293) Ibid. **14**: 206, 1935. (294) Am. J. Obst. & Gynec. **29**: 771, 1935. (295) Ibid. **29**: 120, 1935. (296) Ibid. **31**: 634, 1936. (297) Brit. M. J. **2**: 1190, 1936. (298) Med. Klin. **30**: 1694, 1934. (299) Rev. franç. de gynéc. **30**: 1003, 1935. (300) Zentralbl. f. Gynäk. **58**: 1160, 1934. (301) Orig. in Italian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **28**: 33, 1934. (302) Arch. f. Gynäk. **160**: 481, 1936. (303) Zentralbl. f. Gynäk. **58**: 396, 1935. (304) Monatschr. f. Geburtsh. & Gynäk. **102**: 202, 1936.

(305) Am. J. Obst. & Gynec. **31**: 300, 1936. (306) Surg. Gynec. Obst. **63**: 724, 1936. (307) Orig. in Russian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **31**: 670, 1936. (308) Am. J. Obst. & Gynec. **30**: 18, 1935. (309) Ibid. **25**: 826, 1933. (310) Arch. f. Gynäk. **156**: 35, 1934. (311) Wien. klin. Wchnschr. **49**: 212, 1936. (312) Am. J. Obst. & Gynec. **28**: 179, 1934. (313) J. A. M. A. **105**: 557, 1935. (314) Arch. f. Gynäk. **158**: 173, 1934. (315) Ginecologia **6**: 625, 1935. (316) Am. J. Obst. & Gynec. **26**: 330, 1933. (316a) Orig. in Russian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **31**: 609, 1936. (317) Orig. in Hollandish. Abst. in J. A. M. A. **103**: 80, 1934. (318) Rev. franç. de gynéc. **29**: 573, 1934. (319) Ibid. **29**: 804, 1934. (320) Arch. f. Gynäk. **163**: 141, 1936. (321) Orig. in Italian. Abst. Ber. ü. d. ges. Gynäk. u. Geburtsh. **25**: 483, 1933. (322) Folia gynec.-dermograph. **32**: 377, 1935. (323) Monatschr. f. Geburtsh. u. Gynäk. **97**: 269, 1934. (324) Zentralbl. f. Gynäk. **60**: 2735, 1936. (325) J. A. M. A. **106**: 1625, 1936. (326) Ibid. **106**: 1631, 1936.

(327) Med. Clin. N. A. July, 1935. (328) Orig. in Swedish. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **27**: 180, 1934. (329) Zentralbl. f. Gynäk. **59**: 83, 1935. (330) Orig. in Spanish. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **28**: 206, 1934. (331) Am. J. Obst. & Gynec. **31**: 161, 1936. (332) Med. Klin. **30**: 842, 1934. (333) Rev. franç. de gynéc. **29**: 793, 1934. (334) Endocrinology **19**: 705, 1935. (335) Rev. franç. de gynéc. **27**: 62, 1933. (336) Zentralbl. f. Gynäk. **60**: 370, 1936. (337) Am. J. Obst. & Gynec. **31**: 115, 1936. (338) Orig. in Russian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **27**: 103, 1934. (339) Bull. Soc. radiol. med. France **21**: 561, 1933. (340) Surg. Gynec. Obst. **56**: 322, 1933. (341) Klin. Wchnschr. **14**: 4, 1935. (342) Ann. di ostet. e ginec. **57**: 1613, 1935. (343) Brit. M. J. **1**: 251, 1935. (344) Med. Klin. **30**: 91, 1934. (345) Rev. franç. de gynéc. **29**: 794, 1934. (346) Zentralbl. f. Gynäk. **58**: 568, 1936. (347) Am. J. Obst. & Gynec. **31**: 663, 1936. (348) Wien. klin. Wchnschr. **49**: 289, 1936. (349) Am. J. Obst. & Gynec. **31**: 782, 1936. (350) Rev. franç. de gynéc. **29**: 835, 1934. (351) Zentralbl. f. Gynäk. **59**: 914, 1935. (352) J. Obst. & Gynaec. Brit. Emp. **43**: 487, 1936. (353) Zentralbl. f. Gynäk. **58**: 2608, 1934. (354) Ibid. **60**: 35, 1936.

(355) Orig. in Danish. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **30**: 323, 1935. (356) Wissensch. Gesellsch. Goettingen. Abst. Ber. ü. d. ges. Gynäk. u. Geburtsh. **30**: 529, 1935. (357) Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **31**: 368, 1936. (358) Klin. Wchnschr. **14**: 704, 1935. (359) Monatschr. f. Geburtsh. u. Gynäk. **103**: 185, 1936. (360) München. med. Wchnschr. **81**: 1838, 1934. (361) Brit. M. J. **1**: 1317, 1936. (362) Orig. in Russian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **32**: 676, 1936. (363) Nature **137**: 260, 1936. (364)

Zentralbl. f. Gynäk. **59**: 71, 1935. (365) Wien. klin. Wchnschr. **49**: 525, 1936. (366) Ber. ü. d. ges. Gynäk. u. Geburtsh. **33**: 1, 1936. (367) Orig. in Italian. Abst. in Ber. ü. d. ges. Gynäk. u. Geburtsh. **29**: 520, 1935. (368) Zentralbl. f. Gynäk. **58**: 2413, 1934. (369) Klin. Wchnschr. **14**: 339, 1935. (370) Ibid. **14**: 826, 1935. (371) Bull. Soc. belge de gynéc. **11**: 98, 1935. (372) Orig. in Italian. Abst. in Ber. ü. ges. Gynäk. u. Geburtsh. **31**: 310, 1936. (373) Glandular Physiology and Therapy. A. M. A. p. 467, 1935. (374) Zentralbl. f. Gynäk. **59**: 972, 1935. (375) Ibid. **57**: 2729, 1933. (376) Arch. med. Hydrol. **12**: 290, 1934. (377) Schweiz. med. Wchnschr. **65**: 1168, 1935. (378) Zentralbl. f. Gynäk. **58**: 2373, 1934. (379) Klin. Wchnschr. **12**: 1694, 1933. (380) Brit. M. J. **1**: 888, 1934. (381) Lancet **2**: 356, 1934. (382) Proc. Soc. Exper. Biol. & Med. **32**: 554, 1934. (383) Ibid. **32**: 192, 1935. (384) Am. J. Obst. & Gynec. **29**: 83, 1935. (385) J. A. M. A. **105**: 257, 1935. (386) Lancet **2**: 974, 1936. (387) Ibid. **2**: 842, 1936. (388) Am. J. Obst. & Gynec. **26**: 593, 1933. (389) Surg. Gynec. Obst. **61**: 15, 1935. (390) Compt. rend. Soc. franç. de gynée. **6**: 266, 1936. (391) Surg. Gynec. Obst. **63**: 138, 1936. (392) Arch. f. Gynäk. **163**: 85, 1936. (393) Ztschr. f. Geburtsh. u. Gynäk. **108**: 247, 1934. (394) Med. Klin. **32**: 79, 1936.

3720 Washington Boulevard

Correspondence

To the Editor:

More than ten years have passed since obstetricians have adopted the combination of extracts of the thymus gland and the posterior lobe of the pituitary (''thymophysin''), suggested by me as an agent in labor for use in the stage of dilatation. Every opinion and every method has its followers and its opponents. This applies also to thymophysin.

One can easily understand and appreciate these facts with regard to any remedy. However, certain imputations raised against thymophysin accusing the combination to be ''an unscientific preparation marketed under false claims'' are so serious that they are inconsistent not only with my scientific reputation but also with facts which are supported by a majority of opinions in favor of this oxytocic.

He who quotes publications based upon a few cases as proof for the usefulness or uselessness of a new method must put himself into an untenable position. But if a material is collected from the literature based upon more than 100,000 deliveries reported by well-known clinicians; if a series of publications and theses from well-known university clinics are on record, and if, finally, equally distinguished professors of obstetrics summarize their unanimous judgment on thymophysin, that this preparation represents a distinct progress in the therapeutic armamentarium of the obstetrician, then these facts should be considered evidence of its value.

More than 100 papers dealing with thymophysin have been published in acceptable medical journals.

These judgments, at any rate, together with extensive evidence furnished in the reports of other observers, may induce the obstetricians of the United States, to whose scientific judgment I attach special importance, themselves to test the combination of extracts of the thymus gland and the posterior lobe of the pituitary in a larger number of deliveries.

Miklos Temesvary, M.D.

Buda-Pesth,
August, 1937.

Note: An extensive bibliography dealing with the employment of this preparation and appended to the above communication, cannot be included for lack of space.

Editor.

Books Received

CHILDREN HANDICAPPED BY CEREBRAL PALSY. Psychological factors in management. By Elizabeth Evans Lord, Ph.D., psychologist to Children's Hospital, Boston, etc. With a medical explanation by Bronson Crothers, M.D. The Commonwealth Fund, New York, 1937.

MEDIKAMENTOESE BEKAEMPFUNG DER INTRAUTERINEN ASPHYXIE. Von Dr. med. habil. H. Nevinny, Universitaets-Frauenklinik, Koenigsberg. Mit 48 Textabbildungen, 104 Seiten. Ferdinand Enke, Stuttgart, 1937.

EMOTIONAL ADJUSTMENT IN MARRIAGE. By Le Mon Clark, M.D., assistant in obstetrics and gynecology, University of Illinois College of Medicine. 261 pages. The C. V. Mosby Company, St. Louis, 1937.

THERAPIE DER FRAUENKRANKHEITEN. Von Professor Dr. W. Benthin, Koenigsberg i.P. Zweite, neubearbeitete Auflage. Mit 23 Abbildungen im Text, 219 Seiten. Urban & Schwarzenberg, Berlin und Wien, 1937.

MATERNAL CARE. The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by the Committee on Maternal Welfare, Inc. Dr. Fred L. Adair, Editor. The University of Chicago Press, Chicago, Ill.

THE ENDOCRINES IN OBSTETRICS AND GYNECOLOGY. By Raphael Kurzrok, Ph.D., M.D., associate in obstetrics and gynecology, College of Physicians and Surgeons, Columbia University. Illustrated, 488 pages. Williams and Wilkins Company, Baltimore, 1937.

GETTING READY TO BE A MOTHER. By Carolyn Conant van Blarcom, R.N. Third edition, revised. With 97 illustrations, 305 pages. The Macmillan Company, New York, 1937.

TEXTBOOK OF SURGICAL NURSING. By Henry S. Brookes, Jr., M.D., instructor in clinical surgery, Washington University School of Medicine, etc. With 233 illustrations, 636 pages. The C. V. Mosby Company, St. Louis, 1937.

OBSTETRIC AND GYNECOLOGIC NURSING. By Frederick H. Falls, M.D., professor of obstetrics and gynecology, University of Illinois, College of Medicine, etc., and Jane R. McLaughlin, supervisor of the Department of Obstetrics and Gynecology, Research and Educational Hospital, etc. With 83 illustrations, 492 pages. The C. V. Mosby Company, St. Louis, 1937.

SYNOPSIS OF GYNECOLOGY. By Harry Sturgeon Crossen, professor emeritus of clinical gynecology, Washington University School of Medicine, etc., and Robert James Crossen, assistant professor of clinical gynecology and obstetrics, Washington University School of Medicine, etc. Second edition. With 106 illustrations, 247 pages. The C. V. Mosby Company, St. Louis, 1937.

LIGHT THERAPY. By Frank Hammond Krusen, associate professor of Physical Medicine, The Mayo Foundation, University of Minnesota, etc. Second edition, revised and enlarged. With 42 illustrations, 238 pages. Paul B. Hoeber, Inc., New York, 1937.

Items

Pittsburgh Obstetrical and Gynecological Society

At a regular meeting of the Pittsburgh Obstetrical and Gynecological Society held on October 11, the following officers were installed: President, Dr. Paul Titus, Vice-President, Dr. S. A. Chalfant.

British College of Obstetricians and Gynecologists

At a convocation held in the "College House" in London, on October 22, 1937, Dr. George Gray Ward, of New York, Emeritus Professor of Obstetrics and Gynecology of Cornell University and Chief Surgeon of the Woman's Hospital, was inducted as an Honorary Fellow of this English institution. This distinction has been conferred previously upon American physicians in only two instances, on Dr. J. Whitridge Williams, of Baltimore, in 1931, and Dr. William P. Graves, of Boston, in 1932.

American Board of Obstetrics and Gynecology

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 6, 1937, and Saturday, February 5, 1938. Application for admission to these examinations must be filed on an official application form in the office of the Secretary at least sixty days prior to these dates.

The general oral, clinical and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1938.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

Central Association of Obstetricians and Gynecologists

The Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists was held at the Hotel Adolphus in Dallas, Texas, October 14 to 17, in connection with a meeting of the Texas Association of Obstetricians and Gynecologists. Dr. John A. Kolmer, of Philadelphia, was the guest speaker of the Texas Association and Dr. C. Macfie Campbell, of Cambridge, Mass., was the guest speaker of the Central Association.

Minneapolis has been chosen as the meeting place in 1938, and the Officers and Executive Committee personnel for the coming year are as follows: *President,* Robert D. Mussey; *President-Elect,* Ralph A. Reis; *Vice-President,* William T. Black; *Secretary-Treasurer,* William F. Mengert; *Assistant Secretary,* Earl C. Sage.

INDEX TO VOLUME 34

AUTHORS INDEX*

A

ADAIR, FRED L., AND WATTS, RUTH M., Study of hormonal content of ovarian cyst fluids, 799

ANDERSON, DAVID FYFE, (WITH NOVAK, EMIL), Sarcoma of uterus, 740

ANDERSON, MILFORD X., AND SHELDON, EVERETT A., Granulosa cell carcinoma of ovary in child of three years and nine months, 119

ARMSTRONG, MERVYN V., Angiomatosis retinae (Von Hippel's disease, Lindau's disease) complicated by pregnancy, 494

B

BAER, JOSEPH L., REIS, RALPH A., AND LAEMLE, ROBERT M., Prolapse of uterus—shifting trends in treatment, 827

BEHM, KARL H., (WITH TRITSCH, JOHN E.), Clinical experience with a new ergot alkaloid), 676

BERKOW, SAMUEL GORDON, Status of biometry in endocrine diagnosis, 114

BIERMAN, WILLIAM, AND HOROWITZ, EDWARD A., Gonorrhea in female treated by combined heating technique, 68

BILL, ARTHUR H., Analgesia and anesthesia and their bearing upon problem of shortened labor, 868

BISHOP, ELIOT, Operative methods of sterilization in female, 505

BLAKELY, STUART B., Diagnosis of sex of human fetus in utero, 322

BREWER, JOHN I., AND FITZGERALD, JAMES E., Six normal and complete presomite human ova, 210

BROWN, WILLIS (WITH MILLER, NORMAN F.), Surgical treatment of complete perineal tears in female, 196

BRUNER, J. M., ROSEBROOK, L. E., AND CUSHMAN, G. W., Photographic records of cervix uteri, 1027

BUBIS, J. L., Retrograde cystocele operation, 225

BUTTERWORTH, J. S., (WITH TRAUT, HERBERT F.), Theca, granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary, 987

C

CHEATHAM, GOODE R., Atelectasis as a complication of obstetric analgesia, 166

CLINTON, W. R., (WITH SIDDALL, R. S.), Lymphangioma of ovary, 306

COHEN, MORTIMER, (WITH HUGGINS, RALEIGH R., AND HARDEN, BOYD), True hermaphroditism in man with an endocrinologic study, 136

COLLETT, MARY E., SMITH, JOSEPH T., WERTENBERGER, GRACE E., HARLOR, D. M., REED, FAITH W., AND LONG, SARA J., Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639

COMPTON, BEVERLEY C., Malignancy of granulosa cell tumors, 85

COSGROVE, S. A., Surgical complications of pregnancy, 469

CRABTREE, E. GRANVILLE, PRATHER, GEORGE C., AND PRIEN, EDWIN L., End-results of urinary tract infections associated with pregnancy, 405

CUSHMAN, G. W., (WITH BRUNER, J. M., AND ROSEBROOK, L. E.), Photographic records of cervix uteri, 1027

D

DANFORTH, W. C., Carcinoma of cervix during pregnancy, 365

DAVIS, M. EDWARD, (WITH KOFF, ARTHUR K.), Mechanism of prolongation of pregnancy in rabbit, 26

DECOSTA, EDWIN J., AND REIS, RALPH A., Oral administration of paraldehyde for relief of pain during labor, 448

DE SNOO, K., Prevention of eclampsia, 911

DOUGLAS, R. GORDON, Hypertension, nephritis, and toxemias of pregnancy, 565

DOUGLASS, MARION, (WITH FALLON, F. S.), A new type of syringe adapted for treatment of endocervicitis, 170

DRABKIN, CHARLES, AND GOLDSCHMIDT, SIEGFRIED, Chemical determination of pregnancy by Visscher-Bowman technique, 634

E

EASTMAN, NICHOLSON J., Vascular factor in toxemias of late pregnancy, 549

EHRENFEST, HUGO, Menstruation and its disorders, 530, 699, 1051

F

FALLON, F. G., AND DOUGLASS, MARION, A new type of syringe adapted for treatment of endocervicitis, 170

FALLS, FREDERICK H., Actinomycosis of ovary, 1033

FINOLA, GEORGE C., TRUMP, RUTH A., AND GRIMSON, MOZELLE, Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother, 955

*July, pp. 1-182; August, pp. 183-364; September, pp. 365-548; October, pp. 549-730; November, pp. 731-910; December, pp. 911-1092.

FITZGERALD, JAMES E., (WITH BREWER, JOHN I.), Six normal and complete presomite human ova, 210
FRANKENTHAL, LESTER E., JR., (WITH KOBAK, ALFRED J.), Treatment of cervicovaginitis in children with silver picrate suppositories, 292
FRAZELL, E. L., (WITH HEALY, WILLIAM P.), Method and results of treatment in carcinoma of cervix at Memorial Hospital, 593

G

GAINES, JOSEPH A., Massive puberty hypertrophy of breasts, 130
GOLDSCHMIDT, SIEGFRIED, (WITH DRABKIN, CHARLES), Chemical determination of pregnancy by Visscher-Bowman technique, 634
GOODALL, J. R., AND POWER, R. M. H., Modification of Le Fort operation for increasing its scope, 968
GOUGH, JAMES A., Aberrant suprarenal gland tissue in broad ligament, 1040
—, Study of five patients with chorionepithelioma, 267
GRAD, HERMANN, Bissell operation for cystocele, 589
GRIER, ROBERT M., Maternal morbidity, 298
—, Study of 100 consecutive cases of ectopic pregnancy, 103
GRIMSON, MOZELLE, (WITH FINOLA, GEORGE C., AND TRUMP, RUTH A.), Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother, 955
GUTTMACHER, ALAN F., Analysis of 521 cases of twin pregnancy, 76

H

HAMILTON, BUFORD G., Fear, 183
HARDEN, BOYD, (WITH HUGGINS, RALEIGH R., AND COHEN, MORTIMER), True hermaphroditism in man with an endocrinologic study, 136
HARLOR, D. M., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
HARRAR, JAMES A., Worth-while surgery in newborn, 661
HAUPTMAN, H., (WITH ROYSTON, G. D., AND JENSEN, JULIUS), Tuberculosis and pregnancy, 284
HEALY, WILLIAM P., AND FRAZELL, E. L., Methods and results of treatment in carcinoma of cervix at Memorial Hospital, 593
HELLMAN, ALFRED M., AND MUSA, GEORGE, Studies on dried blood serum of women, 656
HESSELTINE, H. CLOSE, Biologic and clinical import of vulvovaginal mycoses, 855
—, Experimental and clinical therapy of vulvovaginal mycoses, 439
HOROWITZ, EDWARD A., (WITH BIERMAN, WILLIAM), Gonorrhea in female treated by combined heating technic, 68
HUGGINS, RALEIGH R., COHEN, MORTIMER, AND HARDEN, BOYD, True hermaphroditism in man, with an endocrinologic study, 136
HUNNER, GUY L., Unusual obstetric injury causing detachment of bladder and urethra from symphysis pubis and complete epispadias, 840
HUNT, ARTHUR B., AND MUSSEY, ROBERT D., Delivery following stillbirth from dystocia in previous pregnancies, 310

I

INGRAHAM, HAROLD C., AND ROSEN, JAMES ALAN, Obstetric analgesia with acid alurate in rectal ether oil, 672
IRVING, FREDERICK C., Conservative treatment of premature separation of normally implanted placenta, 881

J

JAMES, H. C., Unilateral gonorrheal salpingitis in bicornuate uterus, 1045
JAVERT, CARL T., Erythroblastosis fetalis as a cause of infantile mortality, 1042
JENSEN, JULIUS, (WITH ROYSTON, G. D., AND HAUPTMAN, H.), Tuberculosis and pregnancy, 284

K

KANTER, A. E., Ovarian pregnancy, 1035
KAPLAN, IRA I., Sterilization by irradiation, 507
—, Study of end-results of treatment of amenorrhea and sterility by radiation of 128 married women over a period of 12 years, 420
KEENE, FLOYD E., AND PAYNE, FRANKLIN L., Treatment of functional uterine hemorrhage, 688
KENNEDY, FOSTER, Sterilization and eugenics, 519
KENNEDY, WILLIAM T., Incontinence of urine in female, urethral sphincter mechanism, damage of function, and restoration of control, 576
KLEMPNER, EMANUEL, Ureterohydronephrosis resulting from pelvic inflammatory disease, 125
KOBAK, ALFRED J., AND FRANKENTHAL, LESTER E., JR., Treatment of cervicovaginitis in children with silver picrate suppositories, 292
KOFF, ARTHUR K., AND DAVIS, M. EDWARD, Mechanism of prolongation of pregnancy in rabbit, 26
KOMAROMY, GEZA G., Tetanus associated with criminal abortion, 687
KOPP, MARIE E., Eugenic sterilization laws in Europe, 499
KOTZ, JACOB, AND PARKER, ELIZABETH, Primary dysmenorrhea—an endocrine problem, 38
KRIGBAUM, ROY E., An aid in study of sterility, 1046
KROHN, LEON, LACKNER, JULIUS E., AND SOSKIN, SAMUEL, Effect of ovarian hormones on human (nonpuerperal) uterus, 379
—, (WITH LACKNER, JULIUS E., AND SOSKIN, SAMUEL), Etiology and treatment of primary dysmenorrhea, 248

L

LABATE, JOHN S., AND REYNOLDS, SAMUEL R. M., Sensory pathways of ovarian plexus, 1
LACKNER, JULIUS E., KROHN, LEON, AND SOSKIN, SAMUEL, Etiology and treatment of primary dysmenorrhea, 248
—, (WITH KROHN, LEON, AND SOSKIN, SAMUEL), Effect of ovarian hormones on human (nonpuerperal) uterus, 379

LAEMLE, ROBERT M., (WITH BAER, JOSEPH L., AND REIS, RALPH A.), Prolapse of uterus, 827
LAMB, ARTHUR E., Heart disease in pregnancy, 456
LONG, SARA, J., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
LUIKART, RALPH, Modification of Kielland, Simpson, and Tucker-McLane forceps to simplify their use and improve function and safety, 686
LUTZ, MARTIN H., Ectopic gestation following Pomeroy sterilization, 497

M

MACGREGOR, ARTHUR S., Abdominal pregnancy near term, operation and hormonal studies of blood and urine with placenta left in situ, 1030
MATTHEWS, HARVEY B., Continuous auscultation of fetal heart by means of amplifying stethoscope, 898
MAYER, MAX D., Status of psychotherapy in gynecologic practice, 47
MCWILLIAMS, WILLIAM J., Legal considerations for physician, 615
MILLER, JAMES RAGLAN, Testicular tubular adenoma (Pick), 680
MILLER, LEON, Diagnosis of extrauterine pregnancy, 109
MILLER, NORMAN F., AND BROWN, WILLIS, Surgical treatment of complete perineal tears in female, 196
MINTZ, MAURICE E., Treatment of obstructed fallopian tubes in sterility by diathermy and tubal insufflation, 93
MURPHY, DOUGLAS P., Etiology of congenital malformations in light of biologic statistics, 890
MUSA, GEORGE, (WITH HELLMAN, ALFRED M.), Studies on dried blood serum of women, 656
MUSSEY, ROBERT D., (WITH HUNT, ARTHUR B.), Delivery following stillbirth from dystocia in previous pregnancies, 310

N

NOVAK, EMIL, Some less generally recognized aspects of gynecologic endocrinology, 237
—, AND ANDERSON, DAVID FYFE, Sarcoma of uterus, 740

P

PARDEE, HAROLD E. B., Cardiac functional capacity as an aid to prognosis during pregnancy, 557
PARKER, ELIZABETH, (WITH KOTZ, JACOB), Primary dysmenorrhea—an endocrine problem, 38
PASTORE, JOHN B., A satisfactory leg support for lithotomy position, 168
PAYNE, FRANKLIN L., Clinical significance of endometrial hyperplasia, 762
—, (WITH KEENE, FLOYD E.), Treatment of functional uterine hemorrhage, 688
PHANEUF, LOUIS E., Voluminous hernia of culdesac of Douglas treated by total colpectomy, 152
POSNER, A. CHARLES, Purpura hemorrhagica complicating puerperium, 155
POTTER, SAMUEL B., Incidence of trichomonas vaginalis infections, 169
POWER, R. M. H., (WITH GOODALL, J. R.), Modification of Le Fort operation for increasing its scope, 968
PRATHER, GEORGE C., (WITH CRABTREE, E. GRANVILLE, AND PRIEN, EDWIN L.), End-results of urinary tract infections associated with pregnancy, 405
PRIEN, EDWIN L., (WITH CRABTREE, E. GRANVILLE, AND PRATHER, GEORGE C.), End-results of urinary tract infections associated with pregnancy, 405

R

REED, FAITH, W., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639
REID, DUNCAN E., (WITH TEEL, HAROLD M.), Eclampsia and its sequelae, 12
REIS, RALPH A., Intestinal obstruction complicated by pregnancy at term, 1038
—, (WITH BAER, JOSEPH L., AND LAEMLE, ROBERT M.), Prolapse of uterus, 827
—, (WITH DECOSTA, EDWIN J.), Oral administration of paraldehyde for relief of pain during labor, 448
REYNOLDS, SAMUEL R. M., (WITH LABATE, JOHN S.), Sensory pathways of ovarian plexus, 1
RICHARDSON, EDWARD H., An efficient composite operation for uterine prolapse and associated pathology, 814
RIES, EMIL, Episacroiliac lipoma, 490
ROSEBROOK, L. E., (WITH BRUNER, J. M., AND CUSHMAN, G. W.), Photographic records of cervix uteri, 1027
ROSEN, JAMES ALAN, (WITH INGRAHAM, HAROLD C.), Obstetric analgesia with acid alurate in rectal ether oil, 672
ROSS, ROBERT A., Observations pertinent to gonadotropic therapy in gynecology, 780
ROYSTON, G. D., JENSEN, JULIUS, AND HAUPTMAN, H., Tuberculosis and pregnancy, 284

S

SAGE, EARL C., Missed abortion—a hematoma mole, 163
SALMON, UDALL J., Parametrial fixation operation for uterine prolapse, 58
SCHEFFEY, LEWIS C., AND THUDIUM, WILLIAM J., Experience in treatment of carcinoma of fundus of uterus, 1006
SCHENCK, SAMUEL B., Correspondence, 181
SCHILLER, WALTER, Pathology of cervix, 430
SCHMITZ, HERBERT E., Mortality and complications of 3,129 supracervical hysteromyomectomies, 480
SEEGERS, WALTER H., Nitrogen balance of a young primipara, 1019
SERBIN, WILLIAM B., Splenomegaly in pregnancy, 486
SHELDON, EVERETT A., (WITH ANDERSON, MILFORD X.), Granulosa cell carcinoma of ovary in child of three years and nine months, 119
SIDDALL, R. S., AND CLINTON, W. R., Lymphangioma of ovary, 306
SIEGLER, SAMUEL L., Triplet pregnancy with papyraceous fetus, 1023

SMITH, FRANK R., Effect of pregnancy on malignant tumors, 616

SMITH, JOSEPH T., (WITH COLLETT, MARY E. ET AL.),Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639

SMYTHE, FRANK WARD, Ten-year statistical report of carcinomas of cervix, 317

SOSKIN, SAMUEL (WITH KROHN, LEON, AND LACKNER, JULIUS E.), Effect of ovarian hormones on human (nonpuerperal) uterus, 379

—, (WITH LACKNER, JULIUS E., AND KROHN, LEON), Etiology and treatment of primary dysmenorrhea, 248

SPIELMAN, FRANK, Diffuse squamous cell carcinoma of uterus, 159

T

TAUSSIG, FRED J., Story of prenatal care, 731

TEEL, HAROLD M., AND REID, DUNCAN E., Eclampsia and its sequelae, 12

THOMS, HERBERT, Uses and limitations of roentgen pelvimetry, 150

THUDIUM, WILLIAM J., (WITH SCHEFFEY, LEWIS C.), Experience in treatment of carcinoma of fundus of uterus, 1006

TRAUT, HERBERT F., Pyeloureteritis in pregnancy, 392

—, AND BUTTERWORTH, J. S., Theca granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary, 987

TRITSCH, JOHN E., AND BEHM, KARL H., Clinical experience with a new ergot alkaloid, 676

TRUMP, RUTH A., (WITH FINOLA, GEORGE C., AND GRIMSON, MOZELLE), Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother, 955

U

URDAN, BENJAMIN E., Three cases of placenta previa following tubal inflation, 142

W

WATSON, B. P., Sterilization from point of view of obstetrician and gynecologist, 512

WATTS, RUTH M., (WITH ADAIR, FRED L.), Study of hormonal content of ovarian cyst fluids, 799

WERTENBERGER, GRACE E., (WITH COLLETT, MARY E. ET AL.), Effect of estrin upon basal metabolism rate and nervous symptoms of ovariectomized women, 639

WILLIAMS, PHILIP F., Stillbirth problem, 940

WILSON, KARL M., Pregnancy complicated by ovarian and parovarian tumors, 977

WIMPFHEIMER, SEYMOUR, Menstrual fistula (tubo-abdominal), 146

WOOD, GLENN A., Analysis of 300 consecutive cases of primary cervical repair, 606

WYCKHOFF, JOHN, Sterilization from standpoint of internist, 520

SUBJECT INDEX*

A

Abdominal pregnancy near term, operation and hormonal studies of blood and urine with placenta left in situ (MacGregor), 1030
Aberrant suprarenal gland tissue in broad ligament (Gough), 1040
Abortion, criminal, tetanus associated with (Komaromy), 687
missed—a hematoma mole (Sage), 163
Abstracts, carcinoma, 349
cesarean section, 901
miscellaneous, 11, 25, 46, 67, 84, 102, 129, 141, 158, 195, 209, 247, 266, 316, 391, 404, 419, 455, 498, 575, 615, 633, 638, 679, 685, 939, 976, 1037, 1047
Acid alurate in rectal ether oil, obstetric analgesia with (Ingraham and Rosen), 672
Actinomycosis of ovary (Falls), 1033
Adenocarcinoma of cervix (Norris), 351 (Abst.)
Adenoma, testicular tubular (Pick) (Miller), 680
Advisory Board for Medical Specialties, item of, 364
Alkaloid, ergot, clinical experience with a new (Tritsch and Behm), 676
Amenorrhea and sterility, treatment of, by radiation (Kaplan), 420
treatment of undernutrition and secondary (Vogt), 360 (Abst.)
American Board of Obstetrics and Gynecology, items of, 181, 364, 547, 730, 909, 1078
Gynecological Society, item of, 181
number, 731-910, 911, 968, 977
Analgesia and anesthesia and their bearing upon problem of shortened labor (Bill), 868
obstetric, atelectasis as a complication of (Cheatham), 166
with acid alurate in rectal ether oil (Ingraham and Rosen), 672
Anesthesia and analgesia and their bearing upon problem of shortened labor (Bill), 868
for cesarean section (Brindeau), 903, (Ginglinger), 903 (Absts.)
spinal, cesarean section performed under, avoidance of complications in (Thiessen), 906 (Abst.)
Angiomatosis retinae complicated by pregnancy (Armstrong), 494
Arbeitsphysiologic der Schwangerschaft (Staehler), 177 (B. Rev.)
Aschheim-Zondek test for pregnancy, method for ovarian transplantation on rabbits used for (Campbell), 363 (Abst.)
Atelectasis as a complication of obstetric analgesia (Cheatham), 166
Auscultation, continuous, of fetal heart by means of amplifying stethoscope (Matthews), 898
Avitaminosis in coli bacillus infections of pregnancy, rôle of (Courtois et al.), 129 (Abst.)

B

Baby and growing child (Fischer), 179 (B. Rev.)
Basal metabolism rate, effect of estrin upon, and nervous symptoms of ovariectomized women (Collett et al.), 639
Being born (Strain), 178 (B. Rev.)
Bicornuate uterus, unilateral gonorrheal salpingitis in (James), 1045
Biologic statistics, congenital malformations in light of, etiology of (Murphy), 890
Birth control in India (Pillay), 25 (Abst.)
growth before, rate of (Buchner), 195 (Abst.)
Bissell operation for cystocele (Grad), 589
Bleeding, functional puberty, etiology of, and treatment by hormonal therapy (Witherspoon and Collins), 363 (Abst.)
in late pregnancy (Waters), 455 (Abst.)
uterine, in preclimacterium, treatment of (Joachimovits), 362 (Abst.)
Blood and urine, hormonal studies of, abdominal pregnancy near term, operation and, with placenta left in situ (MacGregor), 1030
cholesterin and ovarian function (Barsony), 976 (Abst.)
serum, dried, of women, studies on (Hellman and Musa), 656
new modification of Friedman test using (Di Gioia), 1037 (Abst.)
Blutung und Fluor (Runge), 339 (B. Rev.)
Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother (Finola, Trump, and Grimson), 955
Book reviews, 172, 336
Books received, 729, 1077
Born, being (Strain), 178 (B. Rev.)
Breast, hypertrophy of, massive puberty (Gaines), 130
British College of Obstetricians and Gynecologists, item of, 1078
Broad ligament, aberrant suprarenal gland tissue in (Gough), 1040
Brooklyn Gynecological Society, transactions of, 528, 698, 1048

C

Cancer, cervical, microscopic diagnosis, does, afford a prognostic guide in (Wetterdal), 350 (Abst.)
of body of uterus after irradiation for metrorrhagia (Fournier), 355 (Abst.)
of cervix (Ulrich), 352 (Abst.)
advanced, treated with acetone and x-radiation (Mackenzie), 356 (Abst.)
after subtotal hysterectomy (Séjournet), 354 (Abst.)
in young women (Döderlein), 353 (Abst.)
uteri (Stout), 353 (Abst.)
radiotherapy of (Mackenzie), 356 (Abst.)
of female genitalia, surgical treatment of (Salacz), 357 (Abst.)
Cancerization of fibroids (Barthélemy), 355 (Abst.)
Carcinoma, 349 (Absts.)
cervices, radium treatment of, corporeal recurrence after (Malpas), 356 (Abst.)
genital, therapy of, relation between histology, prognosis and (Feldwig), 350 (Abst.)

*July, pp. 1-182; August, pp. 183-364; September, pp. 365-548; October, pp. 549-730; November, pp. 731-910; December, pp. 911-1092.

Carcinoma—Cont'd
granulosa cell, of ovary in child of three years and nine months (Anderson and Sheldon), 119
of cervix (Auer), 358 (Abst.)
during pregnancy (Danforth), 365
following supravaginal hysterectomy, risk of (Fahndrich), 354 (Abst.)
methods and results of treatment in, at Memorial Hospital (Healy and Frazell), 593
ten-year statistical report of (Smythe), 317
uteri (Henriksen), 352 (Abst.)
relation of parity to (Tompkins), 353 (Abst.)
of corpus uteri, relationship of late menstruation to (Crossen and Hobbs), 352 (Abst.)
of fundus of uterus, experience in treatment of (Scheffey and Thudium), 1006
of uterus, modern treatment of (Dickinson), 355 (Abst.)
of vulva, treatment of (Carranza), 357 (Abst.)
reaction, Klein, (Grögler), 349, (Reimers), 349 (Absts.)
squamous cell, diffuse, of uterus (Spielman), 159
Cardiac functional capacity as an aid to prognosis during pregnancy (Pardee), 557
Central Association of Obstetricians and Gynecologists, items of, 548, 1078
papers of, 183-321
presidental address, 183
Cervical cancer, microscopic diagnosis, afford a prognostic guide in, does, (Wetterdal), 350 (Abst.)
cesarean section, rupture of scar during labor (Fournier and Estienny), 908 (Abst.)
epithelium, atypical growth induced in (Overholser and Allen), 351 (Abst.)
repair, primary (Wood), 606
stump, sarcoma of (Reckmann), 354 (Abst.)
Cervicovaginitis, treatment of, in children, with silver picrate suppositories (Kobak and Frankenthal), 292
Cervix, adenocarcinoma of (Norris), 351 (Abst.)
cancer of (Ulrich), 352 (Abst.)
advanced, treated with acetone and x-radiation (Mackenzie), 356 (Abst.)
after subtotal hysterectomy (Séjournet), 354 (Abst.)
in young women (Döderlein), 353 (Abst.)
carcinoma of (Auer), 358 (Abst.)
during pregnancy (Danforth), 365
methods and results of treatment in, at Memorial Hospital (Healy and Frazell), 593
ten-year statistical report of (Smythe), 317
pathology of (Schiller), 430
uteri, cancer of (Stout), 353 (Abst.)
radiotherapy of (Mackenzie), 356 (Abst.)
carcinoma of (Henriksen), 352 (Abst.)
relation of parity to (Tompkins), 353 (Abst.)
photographic records of (Bruner, Rosebrook, and Cushman), 1027
precancerous and carcinoid lesions of (Hendriksen), 349 (Abst.)
Cesarean section, 901 (Absts.); (Hoffström), 901 (Abst.)
anesthesia for (Brindeau), 903, (Ginglinger), 903 (Absts.)
Cesarean Section—Cont'd
as method of therapy to maintain circulation of cord (De Guchteneere et al.), 905 (Abst.)
at Boston Lying-In Hospital (Smith), 901 (Abst.)
at William H. Coleman Hospital (Gustafson), 906 (Abst.)
cervical, rupture of scar during labor (Fournier and Estienny), 908 (Abst.)
deaths from (Huessy), 907 (Abst.)
in infected cases (Basden), 906 (Abst.)
in long axis (Bud), 905 (Abst.)
in obstetric practice, present position of (Banister), 903 (Abst.)
in Richmond, Virginia (Hudnall), 902 (Abst.)
indications for (Crichton), 904 (Abst.)
unusual (Andrews and Nichills), 905 (Abst.)
Latzko (Fleischer and Kushner), 905 (Abst.)
low, at Charité Obstetrical Clinic (Bue et al.), 902 (Abst.)
distant consequences of (Trillat), 908 (Abst.)
parotitis after (Voron, Brochier and Magnin), 907 (Abst.)
spontaneous labor after (Andérodias and Péry), 908 (Abst.)
treatment of placenta previa by (Trillat), 903 (Abst.)
lower segment (Riddell), 905 (Abst.)
pathologic results of (Lindsay), 907 (Abst.)
performed under spinal anesthesia, avoidance of complications (Thiessen), 906 (Abst.)
six on same patient (Pemberton), 906 (Abst.)
Chemical determination of pregnancy by Visscher-Bowman technique (Drabkin and Goldschmidt), 634
Cholesterin, blood, and ovarian function (Barsony), 976 (Abst.)
Chorionepithelioma, study of 5 patients with (Gough), 267
Chicago Gynecological Society, item of, 547
transactions of, 528, 1048
Circulation of cord, cesarean section as method of therapy to maintain (De Guchteneere et al.), 905 (Abst.)
Collective review, menstruation and its disorders (Ehrenfest), 530, 699, 1051
Contraception as a therapeutic measure (Moses), 342 (B. Rev.)
Colpectomy, total, voluminous hernia of culdesac of Douglas treated by (Phaneuf), 152
Contraception, medical history of (Hines), 342 (B. Rev.)
Contractions of nonpregnant human uterus, study of (Robertson), 1047 (Abst.)
Cord, circulation of, cesarean section as method of therapy to maintain (De Guchteneere et al.), 905 (Abst.)
Corpus uteri, carcinoma of, relationship of late menstruation to (Crossen and Hobbs), 352 (Abst.)
Correspondence, 181, 526, 730, 1076
Culdesac of Douglas, voluminous hernia of, treated by total colpectomy (Phaneuf), 152
Cyst fluids, ovarian, hormonal content of, study of (Adair and Watts), 799
Cystocele, Bissell operation for (Grad), 589
operation, retrograde (Bubis), 225

D

Delivery following stillbirth from dystocia in previous pregnancies (Hunt and Mussey), 310
Department of practical problems in obstetrics and gynecology, 322, 688
Detachment of bladder and urethra, unusual obstetric injury causing, from symphysis pubis and complete epispadias (Hunner), 840
Diabetes mellitus and pregnancy (Kraus), 129 (Abst.)
Diathermy and tubal insufflation, treatment of obstructed fallopian tubes in sterility by (Mintz), 93
Dicalcium-phosphate and viosterol, bone changes in fetus following administration of, to pregnant mother (Finola, Trump, and Grimson), 955
Dictionary, medical (Stedman), 348 (B. Rev.)
Die Bekaempfung der Eklamptischen Schwangerschafts-Erkrankungen (Siedentopf), 176 (B. Rev.)
Die Gynaekologischen Operationen (Martius), 336 (B. Rev.)
Die Kuenstliche Scheidenbildung aus dem Mastdarm (Schubert), 337 (B. Rev.)
Diet, balanced (Clendening), 348 (B. Rev.)
Discharge, vaginal (Renton), 1047 (Abst.)
Dried blood serum of women, studies on (Hellman and Musa), 656
Dysmenorrhea, endocrinal origin of primary, and its hormonal treatment (Witherspoon), 361 (Abst.)
primary—an endocrine problem (Kotz and Parker), 38
etiology and treatment of (Lackner, Krohn, and Soskin), 248
Dystocia, delivery following stillbirth from, in previous pregnancies (Hunt and Mussey), 310

E

Eclampsia and its sequelae (Teel and Reid), 12
prevention of (De Snoo), 911
Ectopic gestation following Pomeroy sterilization (Lutz), 497
pregnancy, study of 100 consecutive cases of (Grier), 103
Editorial, 1049
Eggs of mammals (Pincus), 346 (B. Rev.)
Emmenin, use of (Goldberg and Lisser), 360 (Abst.)
Emotional problems, single woman and her (Hutton), 340 (B. Rev.)
Endocervicitis, treatment of, a new type of syringe adapted for (Fallon and Douglass), 170
Endocrine diagnosis, status of biometry in (Berkow), 114
problem—primary dysmenorrhea (Kotz and Parker), 38
Endocrinologic study, true hermaphroditism in man with an (Huggins, Cohen, and Harden), 136
Endocrinology, gynecologic, some less generally recognized aspects of (Novak), 237
in modern practice (Wolf), 180 (B. Rev.)
Endometrial hyperplasia, clinical significance of (Payne), 762
Endometriosis of uterine adnexa (Barsony), 419 (Abst.)
Episacroiliac lipoma (Ries), 490
Epispadias, complete, unusual obstetric injury causing detachment of bladder and urethra from symphysis pubis and (Hunner), 840
Ergebnisse der Medizinischen Strahlenforschung (Holfelder et al.), 338 (B. Rev.)
Ergot alkaloid, new, clinical experience with (Tritsch and Behm), 676
Erythroblastosis fetalis as a cause of infantile mortality (Javert), 1042
Estrin, effect of, upon basal metabolism rate and nervous symptoms of ovariectomized women (Collett et al.), 639
Estrogenic principle, effects of large doses of, evaluation of constitutional (Mazer et al.), 362 (Abst.)
Ether oil, rectal, obstetric analgesia with acid alurate in (Ingraham and Rosen), 672
Eugenic sterilization laws in Europe (Kopp), 499
Eugenics and sterilization (Kennedy), 519
Extrauterine pregnancy, diagnosis of (Miller), 109

F

Fallopian tubes in sterility, treatment of obstructed, by diathermy and tubal insufflation (Mintz), 93
Fear (Hamilton), 183
Fetus, bone changes in, following administration of dicalcium-phosphate and viosterol to pregnant mothers (Finola, Trump, and Grimson), 955
Fetal heart, auscultation of, continuous, by means of amplifying stethoscope (Matthews), 898
Fetus, human, diagnosis of sex of, in utero (Blakely), 322
papyraceous, triplet pregnancy with (Siegler), 1023
Fibroid, cancerization of (Barthélemy), 355 (Abst.)
of uterus, pregnancy complicated, triple diagnostic error in case of (Lucchetti), 1039 (Abst.)
Fille ou Garcon (Regnault), 348 (B. Rev.)
First All-India Obstetric and Gynecological Congress, Madras, 178 (B. Rev.)
Fistula, menstrual (Wimpfheimer), 146
Food, fitness and figure (Buckstein), 347 (B. Rev.)
Forceps, Keilland, Simpson, and Tucker-McLane, modification of, to simplify their use and improve function and safety (Luikart), 686
Friedman test, studies of difficulties encountered in (Di Gioia), 1037 (Abst.)
Functional uterine hemorrhage, treatment of (Keene and Payne), 688

G

Genital carcinoma, therapy of, relation between histology, prognosis and (Feldwig), 350 (Abst.)
Genitalia, female, cancer of, surgical treatment of (Salacz), 357 (Abst.)
malignant conditions of, intraspinal injections of alcohol for pain associated with (Greenhill and Schmitz), 358 (Abst.)
mumps and (Bosch), 575(Abst.)
Gestation, ectopic, following Pomeroy sterilization (Lutz), 497

Gland, interstitial, in human beings (Freiman), 685 (Abst.)
tissue, aberrant suprarenal, in broad ligament (Gough), 1040
Gonadotropic stimulation therapy (Zondek), 360 (Abst.)
therapy in gynecology, observations pertinent to (Ross), 780
Gonorrhea in female treated by combined heating technic (Bierman and Horowitz), 68
Gonorrheal salpingitis, unilateral, in bicornuate uterus (James), 1045
Granulosa cell carcinoma of ovary in child of three years and nine months (Anderson and Sheldon), 119
tumors, malignancy of (Compton), 85
theca and lutein, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
Gynecologic endocrinology, some less generally recognized aspects of (Novak), 237
practice, status of psychotherapy in (Mayer), 47
Gynecologist and obstetrician, sterilization from point of view of (Watson), 512
Gynecology, 336 (B. Rev.)
abortion, criminal, tetanus associated with (Komaromy), 687
missed—a hematoma mole (Sage), 163
actinomycosis of ovary (Falls), 1033
adenocarcinoma of cervix (Norris), 351 (Abst.)
adenoma, testicular tubular (Miller), 680
amenorrhea and sterility, treatment of, by radiation (Kaplan), 420
and obstetrics, (Jameson), 336 (B. Rev.)
department of practical problems in, 322, 688
cancer of body of uterus after irradiation for metrorrhagia (Fournier), 355 (Abst.)
of cervix (Ulrich), 352 (Döderlein), 353 (Absts.)
advanced, treated with acetone and x-radiation (Mackenzie), 356 (Abst.)
after subtotal hysterectomy (Séjournet), 354 (Abst.)
uteri (Stout), 353 (Abst.)
radiotherapy of (Mackenzie), 356 (Abst.)
of female genitalia, surgical treatment of (Salacz), 357 (Abst.)
carcinoma granulosa cell, of ovary in child of three years and nine months (Anderson and Sheldon), 119
of cervix (Auer), 358 (Abst.)
during pregnancy (Danforth), 365
methods and results of treatment in, at Memorial Hospital (Healy and Frazell), 593
ten-year statistical report of (Smythe), 317
uteri (Henriksen), 352 (Abst.)
relation of parity to (Tompkins), 353 (Abst.)
of corpus uteri, relationship of late menstruation to (Crossen and Hobbs), 352 (Abst.)
of uterus, modern treatment of (Dickinson), 355 (Abst.)
of vulva, treatment of (Carranza), 357 (Abst.)
squamous cell, diffuse, of uterus (Spielman), 159
cervical repair, primary (Wood), 606
Gynecology—Cont'd
cervicovaginitis, treatment of, in children with silver picrate suppositories (Kobak and Frankenthal), 292
chorionepithelioma, study of 5 patients with (Gough), 267
colpectomy, total, voluminous hernia of culdesac of Douglas treated by (Phaneuf), 152
cystocele, Bissell operation for (Grad), 589
discharge, vaginal (Renton), 1047 (Abst.)
dysmenorrhea, primary—an endocrine problem (Kotz and Parker), 38
etiology and treatment of (Lackner, Krohn, and Soskin), 248
endocervicitis, treatment of, a new type of syringe adapted for (Fallon and Douglass), 170
fibroids, cancerization of (Barthélemy), 355 (Abst.)
fistula, menstrual (Wimpfheimer), 146
for nurses (Crossen and Crossen), 339 (B. Rev.)
gonadotropic therapy in, observations pertinent to (Ross), 780
gonorrhea in female treated by combined heating technique (Bierman and Horowitz), 68
hemorrhage, functional uterine, treatment of (Keene and Payne), 688
hernia, voluminous, of culdesac of Douglas treated by total colpectomy (Phaneuf), 152
hydatid mole in 55-year-old woman (Feenders), 939 (Abst.)
hysterectomy, supravaginal, risk of carcinoma of cervix following (Fahndrich), 354 (Abst.)
hysterotomy for placenta previa in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)
inflammatory disease, pelvic, ureterohydronephrosis resulting from (Klempner), 125
lipoma, episacroiliac (Ries), 490
lymphangioma of ovary (Siddall and Clinton), 306
mole, hematoma—missed abortion (Sage), 163
mycoses, vulvovaginal, biologic and clinical import of (Hesseltine), 855
experimental and clinical therapy of (Hesseltine), 439
operation, Bissell, for cystocele (Grad), 589
cystocele, retrograde (Bubis), 225
for uterine prolapse, an efficient composite, and associated pathology (Richardson), 814
Le Fort, modification of, for increasing its scope (Goodall and Power), 968
parametrial fixation, for uterine prolapse (Salmon), 58
pelvimetry, roentgen, uses and limitations of (Thoms), 150
prolapse of uterus (Baer, Reis, and Laemle), 827
uterine, parametrial fixation operation for (Salmon), 58
purpura hemorrhagica complicating puerperium (Posner), 155
pyeloureteritis in pregnancy (Traut), 392
radiotherapy of cancer of cervix uteri (Mackenzie), 356 (Abst.)
radium treatment of carcinoma cervices, corporeal recurrence after (Malpas), 356 (Abst.)
salpingitis, gonorrheal, unilateral, in bicornuate uterus (James), 1045

Gynecology—Cont'd
sarcoma of cervical stump (Reckmann), 354 (Abst.)
of uterus (Novak and Anderson), 740
sterility and amenorrhea, treatment of, by radiation (Kaplan), 420
study of, an aid in (Krigbaum), 1046
surgical treatment of complete perineal tears in female (Miller and Brown), 196
toxemias, hypertension, and nephritis of pregnancy (Douglas), 565
trichomonas vaginalis infections, incidence of (Potter), 169
tumors, granulosa cell, malignancy of (Compton), 85
malignant, effect of pregnancy on (Smith), 616
ovarian and parovarian, pregnancy complicated by (Wilson), 977
theca, granulosa and lutein cell, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
ureterohydronephrosis resulting from pelvic inflammatory disease (Klempner), 125

H

Heart disease in pregnancy (Lamb), 456
management of (Jensen), 904 (Abst.)
fetal, auscultation of, continuous, by means of amplifying stethoscope (Matthews), 898
Heating technique, combined, gonorrhea in female treated by (Bierman and Horowitz), 68
Hematoma mole—missed abortion (Sage), 163
Hemorrhage, functional uterine, treatment of (Keene and Payne), 688
postclimacteric, and their relation to malignant neoplasms (Wittenbourg and Zlatmann), 352 (Abst.)
Hermaphroditism, true, in man with an endocrinologic study (Huggins, Cohen, and Harden), 136
Hernia, voluminous, of culdesac of Douglas treated by total colpectomy (Phaneuf), 152
Hormonal content of ovarian cyst fluids, study of (Adair and Watts), 799
studies of blood and urine, abdominal pregnancy near term, operation and, with placenta left in situ (MacGregor), 1030
therapy for menstrual disturbances Westman), 358 (Abst.)
treatment by, etiology of functional puberty bleeding and (Witherspoon and Collins), 363 (Abst.)
treatment of dysmenorrhea, primary, endocrinal origin of (Witherspoon), 361 (Abst.)
Hormones, estrogenic and luteal, treatment of amenorrhea by (Vogt), 360 (Abst.)
ovarian and pituitary (Fairlie), 359 (Abst.)
effect of, on human (nonpuerperal) uterus (Krohn, Lackner and Soskin), 379
sex, treatment with female (Neumann), 358 (Abst.)
Hydatid mole in 55-year-old woman (Feenders), 939 (Abst.)
Hydramnios during pregnancy, percutaneous puncture for (Mayer), 498 (Abst.)
Hygiene, woman's, facts and frauds in (Palmer and Greenberg), 340 (B. Rev.)
Hyperplasia, endometrial, clinical significance of (Payne), 762
Hypertension, menopausal (Schaefer), 362 (Abst.)
nephritis, and toxemias of pregnancy (Douglas), 565
Hypertrophy, puberty, massive, of breasts (Gaines), 130 (Abst.)
Hypophysis, implantation of, treatment of amenorrhea by (Vogt), 360 (Abst.)
Hysterectomy, subtotal, cancer of cervix after (Séjournet), 354 (Abst.)
supravaginal, risk of carcinoma of cervix following (Fahndrich), 354 (Abst.)
Hysteromyomectomies, supracervical, mortality and complications of 3,129 (Schmitz), 480
Hysterosalpingography (Lundquist and Runström), 391 (Abst.)
Hysterotomy for placenta previa in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)

I

Incontinence of urine in female (Kennedy), 576
Infant mortality, factors responsible for failure further to reduce, 1049 (Edit.)
Infantile mortality, erythroblastosis fetalis as cause of (Javert), 1042
Infections, trichomonas vaginalis, incidence of (Potter), 169
urinary tract, end-results of, associated with pregnancy (Crabtree, Prather and Prien), 405
Inflation, tubal, placenta previa following (Urdan), 142
Injury, obstetric, unusual, causing detachment of bladder and urethra from symphysis pubis and complete epispadias (Hunner), 840
Insufflation, tubal, treatment of obstructed fallopian tubes in sterility by diathermy and (Mintz), 93
Internist, sterilization from standpoint of (Wyckhoff), 520
International Congress of Obstetrics and Gynecology, item of, 548
Interstitial glands in human beings (Freiman), 685 (Abst.)
Intestinal obstruction complicated by pregnancy at term (Reis), 1038
Intraspinal injections of alcohol for pain associated with malignant conditions of female genitalia (Greenhill and Schmitz), 358 (Abst.)
Intravenous use of gum acacia glucose infusions, severe and fatal reactions following (Studdiford), 615 (Abst.)
Irradiation for metrorrhagia, cancer of body of uterus after (Fournier), 355 (Abst.)
sterilization by (Kaplan), 507
Items, Advisory Board for Medical Specialties, 364
American Board of Obstetrics and Gynecology, 181, 364, 547, 730, 909, 1078
Gynecological Society, 181
British College of Obstetricians and Gynecologists, 1078
Central Association of Obstetricians and Gynecologists, 548, 1078
Chicago Gynecological Society, 547
International Congress of Obstetrics and Gynecology, 548
Mississippi Valley Medical Society, 909
Pittsburgh Obstetrical and Gynecological Society, 1077

K

Kielland forceps, modification of, to simplify their use and improve function and safety (Luikart), 686
Konservative Therapie der Frauenkrankheiten (Kahr), 339 (B. Rev.)

L

Labor, pain during, relief of, oral administration of paraldehyde for (DeCosta and Reis), 448
problem of shortened, analgesia and anesthesia and their bearing upon (Bill), 868
rupture of cervical cesarean section scar during labor (Fournier and Estienny), 908 (Abst.)
spontaneous, after low cesarean section (Andérodias and Péry), 908 (Abst.)
Latzko cesarean section (Fleischer and Kushner), 905 (Abst.)
Le Fort operation, modification of, for increasing its scope (Goodall and Power), 968
Leg support for lithotomy position, satisfactory (Pastore), 168
Legal consideration for physician, relating to sterilization (McWilliams), 516
Les Problèmes D'Oncologie, 347 (B. Rev.)
Lindau's disease complicated by pregnancy (Armstrong), 494
Lipoma, episacroiliac (Ries), 490
Lithotomy position, leg support for, satisfactory (Pastore), 168
Lutein cell tumors, theca and granulosa, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
Lymphangioma of ovary (Siddall and Clinton), 306
Lymphogranuloma inguinale of female urethra (Gray), 247 (Abst.)
Lymphopathia venera, Frei test in, specificity of (Bacon), 158 (Abst.)

M

Malformations, congenital, etiology of, in light of biologic statistics (Murphy), 890
Married, engaged and single (Chideckel), 343 (B. Rev.)
woman (Groves and Ross), 341 (B. Rev.)
Maternal morbidity (Grier), 298
Maternity services (Browne), 67 (Abst.)
Medical classics (Kelly) 343 (B. Rev.)
dictionary (Stedman), 348 (B. Rev.)
history of contraception (Hines), 342 (B. Rev.)
Medicine and mankind, 344 (B. Rev.)
Menopausal hypertension (Schaefer), 362 (Abst.)
Menstrual disturbances, hormonal therapy for (Westman), 358 (Abst.)
fistula (Wimpfheimer), 146
Menstruation and its disorders (Ehrenfest), 530, 699, 1051 (Collect. Rev.)
relationship of late, to carcinoma of corpus uteri (Crossen and Hobbs), 352 (Abst.)
Metabolism rate, basal, effect of estrin upon, and nervous symptoms of ovariectomized women (Collett et al.), 639
Metrorrhagia, irradiation for, cancer of body of uterus after (Fournier), 355 (Abst.)
Midwifery services (Moyes), 141 (Abst.)
Migraine and ovarian deficiency (Glass), 361 (Abst.)
Mississippi Valley Medical Society, item of, 909
Mole, hematoma—missed abortion (Sage), 163
Morbidity, maternal (Grier), 298
Mortality and complications of 3,129 supracervical hysteromyomectomies (Schmitz), 480
infant, factors responsible for failure further to reduce, 1049 (Edit.)
infantile, erythroblastosis fetalis as cause of (Javert), 1042
Mumps and female genitalia (Bosch), 575 (Abst.)
Mycoses, vulvovaginal, biologic and clinical import (Hesseltine), 855
experimental and clinical therapy of (Hesseltine), 439

N

Nel Trentesimo di Fondazione, Della R. Clinica Ostetrico-Ginecologica "Luigi Mangiagalli" di Milano, 177 (B. Rev.)
Neoplasms, malignant, postclimacteric hemorrhages and their relation to (Wittenbourg and Zlatmann), 352 (Abst.)
Nephritis, hypertension, and toxemias of pregnancy (Douglas), 565
Nervous disease, preface to (Cobb), 347 (B. Rev.)
symptoms, effect of estrin upon basal metabolism rate and, of ovariectomized women (Collett et al.), 639
Nevus telangiectaticus and pregnancy (Wirth), 11 (Abst.)
Newborn, surgery in (Harrar), 661
New York Academy of Medicine, section on obstetrics and gynecology, transactions of, 529
Obstetrical Society, transactions of, 527, 698
Nitrogen balance of young primipara (Seegers), 1019
Nurses, gynecology for (Crossen and Crossen), 339 (B. Rev.)
Nursing, pediatric (Zahorsky), 179 (B. Rev.)

O

Obstetric analgesia, atelectasis as a complication of (Cheatham), 166
with acid alurate in rectal ether oil (Ingraham and Rosen), 672
difficulties, management of (Titus), 173 (B. Rev.)
injury, unusual, causing detachment of bladder and urethra from symphysis pubis and complete epispadias (Hunner), 840
practice, cesarean section in, present position of (Banister), 903 (Abst.)
Obstetrical Society of Philadelphia, transactions of, 528, 1048
Obstetrician and gynecologist, sterilization from point of view of (Watson), 512
Obstetrics, 172 (B. Rev.)
and gynecology (Jameson), 336 (B. Rev.)
department of practical problems in, 322, 688
cesarean section, 901 (Abst.); (Hoffström), 901 (Abst.)
anesthesia for (Brindeau), 903, (Ginglinger), 903 (Absts.)
as method of therapy to maintain circulation of cord (De Guchteneere et al.), 905 (Abst.)
at Boston Lying-In Hospital (Smith), 901 (Abst.)

Obstetrics, cesarean section—Cont'd
at William H. Coleman Hospital (Gustafson), 906 (Abst.)
cervical, rupture of scar during labor after (Fournier and Estienny), 908 (Abst.)
deaths from (Huessy), 907 (Abst.)
in infected cases (Basden), 906 (Abst.)
in long axis (Bud), 905 (Abst.)
in obstetric practice, present position of (Banister), 903 (Abst.)
in Richmond, Virginia (Hudnall), 902 (Abst.)
indications for (Crichton), 904 (Abst.)
unusual (Andrews and Nichills), 905 (Abst.)
Latzko (Fleischer and Kushner), 905 (Abst.)
low at Charité Obstetrical Clinic (Bue et al.), 902 (Abst.)
distant consequences of (Trillat), 908 (Abst.)
parotitis after (Voron et al.), 907 (Abst.)
treatment of placenta previa by (Trillat), 903 (Abst.)
lower segment (Riddell), 905 (Abst.)
pathologic results of (Lindsay), 907 (Abst.)
performed under spinal anesthesia, avoidance of complications in (Thiessen), 906 (Abst.)
six on same patient (Pemberton), 906 (Abst.)
delivery following stillbirth from dystocia in previous pregnancies (Hunt and Mussey), 310
eclampsia and its sequelae (Teel and Reid), 12
prevention of (De Snoo), 911
gestation, ectopic following Pomeroy sterilization (Lutz), 497
labor, pain during, relief of, oral administration of paraldehyde for (DeCosta and Reis), 448
shortened, analgesia and anesthesia and their bearing upon problem of (Bill), 868
placenta previa following tubal inflation (Urdan), 142
hysterotomy for, in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)
treatment of, by low cesarean section (Trillat), 903 (Abst.)
practical, manual of (Brown), 175 (B. Rev.)
pregnancy, abdominal, near term, operation and hormonal studies of blood and urine with placenta left in situ (MacGregor), 1030
and tuberculosis (Royston, Jensen, and Hauptman), 284
carcinoma of cervix during (Danforth), 365
complicated by ovarian and parovarian tumors (Wilson), 977
complicating intestinal obstruction (Reis), 1038
ectopic, study of 100 consecutive cases of (Grier), 103
effect of, on malignant tumors (Smith), 616
extrauterine, diagnosis of (Miller), 109
heart disease in (Lamb), 456
hypertension, nephritis, and toxemias of (Douglas), 565
late, toxemias of, vascular factor in (Eastman), 549
mechanism of prolongation of, in rabbit (Koff and Davis), 26
ovarian (Kanter), 1035
Obstetrics, pregnancy—Cont'd
prognosis during, cardiac functional capacity as an aid to (Pardee), 557
pyeloureteritis in (Traut), 392
splenomegaly in (Serbin), 486
surgical complications of (Cosgrove), 469
triplet, with papyraceous fetus (Siegler), 1023
twin, analysis of 521 cases of (Guttmacher), 76
textbook of (Schumann), 172 (B. Rev.)
Williams (Stander), 173 (B. Rev.)
Obstruction, intestinal, complicated by pregnancy at term (Reis), 1038
Oil, rectal ether, obstetric analgesia with acid alurate in (Ingraham and Rosen), 672
Operation, Bissell, for cystocele (Grad), 589
cystocele, retrograde (Bubis), 225
for uterine prolapse, an efficient composite, and associated pathology (Richardson), 814
Le Fort, modification of, for increasing its scope (Goodall and Power), 968
parametrial fixation, for uterine prolapse (Salmon), 58
Operative methods of sterilization in female (Bishop), 505
Oral thrush and vulvovaginitis, cultural and morphologic studies of cryptococci and monilias isolated from (Hopkins and Hesseltine), 209 (Abst.)
Organotherapy, 358 (Absts.)
Ova, presomite human, six normal and complete (Brewer and Fitzgerald), 210
Ovarian and parovarian tumors, pregnancy complicated by (Wilson), 977
and pituitary hormones (Fairlie), 359 (Abst.)
cyst fluids, hormonal content of, study of (Adair and Watts), 799
deficiency, migraine and (Glass), 361 (Abst.)
function, blood cholesterin and (Barsony), 976 (Abst.)
grafts (Massabuán et al.), 141 (Abst.)
hormones, effect of, on human (nonpuerperal) uterus (Krohn, Lackner and Soskin), 379
injections of, prolonged, combined with chronic trauma (Overholser and Allen), 351 (Abst.)
plexus, sensory pathways of (Labate and Reynolds), 1
pregnancy (Kanter), 1035
transplantation on rabbits used for Aschheim-Zondek test for pregnancy (Campbell), 363 (Abst.)
Ovariectomized women, effect of estrin upon basal metabolism rate and nervous symptoms of (Collett et al.), 639
Ovary, actinomycosis of (Falls), 1033
and tube, unilateral failure of development of, in light of biologic and anatomic knowledge (Lartschneider), 46 (Abst.)
granulosa cell carcinoma of, in child of three years and nine months (Anderson and Sheldon), 119
human, theca, granulosa, lutein cell tumors of, and similar tumors of mouse's ovary (Traut and Butterworth), 987
lymphangioma of (Siddall and Clinton), 306
Ovum, death of, pregnancy test in relation to (Bishop), 363 (Abst.)
single and double, twinning, differences in (Guttmacher), 76

P

Pain during labor, relief of, oral administration of paraldehyde for, (DeCosta and Reis), 448
Papyraceous fetus, triplet pregnancy with (Siegler), 1023
Paraldehyde for relief of pain during labor, oral administration of, (DeCosta and Reis), 448
Parametrial fixation operation for uterine prolapse (Salmon), 58
Parotitis after low cesarean section (Voron, et al.), 907 (Abst.)
Parovarian and ovarian tumors, pregnancy complicated by (Wilson), 977
Parturition, an evolutionary factor in (Gillies), 102 (Abst.)
Pastor, physician and patient (Jacoby), 344 (B. Rev.)
Patient and the weather (Peterson), 347 (B. Rev.)
  physician, and pastor (Jacoby), 344 (B. Rev.)
Pediatric nursing (Zahorsky), 179 (B. Rev.)
Pelvic inflammatory disease, ureterohydronephrosis resulting from (Klempner), 125
Pelvimetry, roentgen, uses and limitations of (Thoms), 150
Perineal tears, complete, in female, surgical treatment of (Miller and Brown), 196
Perineum, restoration of, immediate, suture of sphincter with horsehair in (Mahon), 633 (Abst.)
Photographic records of cervix uteri (Bruner, Rosebrook, and Cushman), 1027
Physician, 343 (B. Rev.)
  legal considerations, for, relating to sterilization (McWilliams), 516
  pastor and patient (Jacoby), 344 (B. Rev.)
  true (Johnson), 343 (B. Rev.)
Physiology and pharmacology of pituitary body (Van Dyke), 179 (B. Rev.)
Pineal extract, organotherapeutic researches on (Hofstätter), 361 (Abst.)
Pittsburgh Obstetrical and Gynecological Society, item of, 1077
Pituitary body, physiology and pharmacology of (Van Dyke), 179 (B. Rev.)
  hormones, ovarian and (Fairlie), 359 (Abst.)
Placenta, premature separation of normally implanted, conservative treatment of (Irving), 881
  previa following tubal inflation (Urdan), 142
    hysterotomy for, in Obstetrical Clinic of Lyon (Voron et al.), 902 (Abst.)
    treatment of, by low cesarean section (Trillat), 903 (Abst.)
Placental insertion in mechanism of rupture of uterus (Orrul), 908 (Abst.)
Plexus, ovarian, sensory pathways of (Labate and Reynolds), 1
Polyps, bleeding, of septum (Banssillon and Mounier-Kuh), 25 (Abst.)
Pomeroy sterilization, ectopic gestation following (Lutz), 497
Precocious motherhood (Olsen), 316 (Abst.)
Pregnancy, abdominal, near term, operation and hormonal studies of blood and urine with placenta left in situ (MacGregor), 1030
  and nevus telangiectaticus (Wirth), 11 (Abst.)
Pregnancy—Cont'd
  and tuberculosis (Royston, Jensen, and Hauptman), 284
  bleeding in late (Waters), 455 (Abst.)
  carcinoma of cervix during (Danforth), 365
  chemical determination of, by Visscher-Bowman technique (Drabkin and Goldschmidt), 634
  coli bacillus infections of, rôle of avitaminosis in (Courtois, et al.), 129 (Abst.)
  complicated by fibroid of uterus, triple diagnostic error in case of (Lucchetti), 1039 (Abst.)
    ovarian and parovarian tumors (Wilson), 977
  complicating angiomatosis retinae (Armstrong), 494
    intestinal obstruction (Reis), 1038
  diabetes mellitus and (Kraus), 129 (Abst.)
  ectopic, study of 100 consecutive cases of (Grier), 103
  effect of, on malignant tumors (Smith), 616
  epistaxis during (Banssillon and Mounier-Kuh), 25 (Abst.)
  extrauterine, diagnosis of (Miller), 109
  heart disease in (Lamb), 456
    management of (Jensen), 904 (Abst.)
  influence of, upon development of tar carcinoma in white mice, experimental research upon (Cini), 316 (Abst.)
  late, toxemias of, vascular factor in (Eastman), 549
  mechanism of prolongation of, in rabbit (Koff and Davis), 26
  ovarian (Kanter), 1035
  prognosis during, cardiac functional capacity as an aid to (Pardee), 557
  puncture for hydramnios during, percutaneous (Mayer), 498 (Abst.)
  pyeloureteritis in (Traut), 392
  rupture of symphysis during (Hirsch), 404 (Abst.)
  splenomegaly in (Serbin), 486
  surgical complications of, (Cosgrove), 469
  test in relation to death of ovum (Bishop), 363 (Abst.)
    Visscher-Bowman, experiences with (Schenck and Tran), 526 (Correspondence)
  toxemias of (McIlroy), 175 (B. Rev.)
    hypertension and nephritis (Douglas), 565
  triple, roentgen diagnosis of (Ballard), 526 (Correspondence)
  triplet with papyraceous fetus (Siegler), 1023
  twin, analysis of 521 cases of (Guttmacher), 76
  urinary tract infections associated with (Crabtree, Prather, and Prien), 405
Pregnant mother, administration of dicalcium-phosphate and viosterol to, bone changes in fetus following (Finola, Trump and Grimson), 955
Premature separation of normally implanted placenta, conservative treatment of (Irving), 881
Prenatal care, story of (Taussig), 731
Presomite human ova, six normal and complete (Brewer and Fitzgerald), 210
Primipara, nitrogen balance of a young (Seegers), 1019
Prolapse of uterus (Baer, Reis, and Laemle), 827
  uterine, operation for, an efficient composite, and associated pathology (Richardson), 814

Prolapse, uterine—Cont'd
parametrial fixation operation for (Salmon), 58
Prostitution (Kemp), 339 (B. Rev.)
Psychology of sex (Ellis), 340 (B. Rev.)
Psychotherapy, status of, in gynecologic practice (Mayer), 47
Puberty bleeding, functional, etiology of, and treatment of hormonal therapy (Witherspoon and Collins), 363 (Abst.)
hypertrophy, massive, of breasts (Gaines), 130
Puerperal tetanus, posthysterectomy and (Pulvertaft), 679 (Abst.)
Puerperium, purpura hemorrhagica complicating (Posner), 155
Pyelitis of defloration (Lepontre), 266 (Abst.)
Pyeloureteritis in pregnancy (Traut), 392

R

Radiation in treatment of amenorrhea and sterility (Kaplan), 420
Radiothérapie Gynécologique (Mathey-Cornat), 338 (B. Rev.)
Radiotherapy of cancer of cervix uteri (Mackenzie), 356 (Abst.)
Radium treatment of carcinoma cervices, corporeal recurrence after (Malpas), 356 (Abst.)
Rectal ether oil, obstetric analgesia with acid alurate in (Ingraham and Rosen), 672
Repair, cervical, primary (Wood), 606
Restoration of perineum, immediate, suture of sphincter with horsehair in (Mahon), 633 (Abst.)
Résultats des Greffes Ovariennes (Mocquet and Cotte), 337 (B. Rev.)
Review of new books, 172, 336
Roentgen diagnosis of triple pregnancy (Ballard), 526 (Correspondence)
pelvimetry, uses and limitations of (Thoms), 150
Rupture of scar during labor following cervical cesarean section (Fournier and Estienny), 908 (Abst.)
of uterus, placental insertion in mechanism of (Orrul), 908 (Abst.)

S

Salpingitis, gonorrheal, unilateral, in bicornuate uterus (James), 1045
Sarcoma of cervical stump (Reckmann), 354 (Abst.)
of uterus (Novak and Anderson), 740
Schiller test (Hendriksen), 349 (Abst.)
Sensory pathways of ovarian plexus (Labate and Reynolds), 1
Separation, premature, of normally implanted placenta, conservative treatment of (Irving), 881
Serum, blood, dried, of women, studies on (Hellman and Musa), 656
Sex, diagnosis of, of human fetus in utero (Blakely), 322
hormones, female, treatment with (Neumann), 358 (Abst.)
problems, 340 (B. Rev.)
psychology of (Ellis), 340 (B. Rev.)
Silver picrate suppositories, treatment of cervicovaginitis in children with (Kobak and Frankenthal), 292
Simpson forceps, modification of, to simplify their use and improve function and safety (Luikart), 686
Single, engaged and married (Chideckel), 343 (B. Rev.)
Society transactions, Brooklyn Gynecological Society, 528, 698, 1048
Chicago Gynecological Society, 528, 1048
New York Academy of Medicine, section on obstetrics and gynecology, 529
Obstetrical Society, 527, 698
Obstetrical Society of Philadelphia, 528, 1048
Washington Gynecological Society, 529
Sphincter, suture of, with horsehair in immediate restoration of perineum (Mahon), 633 (Abst.)
Spinal anesthesia, cesarean section performed under, avoidance of complications in (Thiessen), 906 (Abst.)
Splenomegaly in pregnancy (Serbin), 486
Squamous cell carcinoma, diffuse, of uterus (Spielman), 159
Sterility and amenorrhea, treatment of, by radiation (Kaplan), 420
fallopian tubes in, treatment of, obstructed, by diathermy and tubal insufflation (Mintz), 93
study of, an aid in (Krigbaum), 1046
Sterilization and eugenics (Kennedy), 519
by irradiation (Kaplan), 507
from point of view of obstetrician and gynecologist (Watson), 512
from standpoint of internist (Wyckhoff), 520
in female, operative methods of (Bishop), 505
laws, eugenic, in Europe (Kopp), 499
legal considerations for physician (McWilliams), 516
Pomeroy, ectopic gestation following (Lutz), 497
symposium on, 499-525
Stethoscope, amplifying, continuous auscultation of fetal heart by means of (Matthews), 898
Stillbirth, delivery following, from dystocia in previous pregnancies (Hunt and Mussey), 310
problem (Williams), 940
Suppositories, silver picrate, treatment of cervicovaginitis in children with (Kobak and Frankenthal), 292
Supracervical hysteromyomectomies, mortality and complications of 3,129 (Schmitz), 480
Suprarenal gland tissue, aberrant, in broad ligament (Gough), 1040
Supravaginal hysterectomy, risk of carcinoma of cervix following (Fahndrich), 354 (Abst.)
Surgery in newborn (Harrar), 661
postgraduate, 345 (B. Rev.)
Surgical complications of pregnancy (Cosgrove), 469
treatment of complete perineal tears in female (Miller and Brown), 196
Suture of sphincter with horsehair in immediate restoration of perineum (Mahon), 633 (Abst.)
Symphysis pubis, detachment of bladder and urethra from, unusual obstetric injury causing, and complete epispadias (Hunner), 840
rupture of, spontaneous, during pregnancy (Hirsch), 404 (Abst.)
Syphilis and its treatment (Hinton), 344 (B. Rev.)
Syringe adapted for treatment of endocervicitis, a new type of (Fallon and Douglass), 170

T

Tear, perineal, complete, in female, surgical treatment of (Miller and Brown), 196
Test, Friedman, studies of difficulties encountered in (Di Gioia), 1037 (Abst.)
pregnancy, in relation to death of ovum (Bishop), 363 (Abst.)
Testicular tubular adenoma (Pick) (Miller), 680
Tetanus associated with criminal abortion (Komaromy), 687
puerperal, posthysterectomy and (Pulvertaft), 679 (Abst.)
Theca cell, granulosa, lutein cell tumors of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
Therapeutica das Syndromes Gravido-Puerperaes (de Camargo), 176 (B. Rev.)
Tissue, aberrant suprarenal gland, in broad ligament (Gough), 1040
Toxemias of late pregnancy, vascular factor in (Eastman), 549
of pregnancy (McIlroy), 175 (B. Rev.)
hypertension and nephritis (Douglas), 565
Trichomonas vaginalis infections, incidence of (Potter), 169
Triplet pregnancy with papyraceous fetus (Siegler), 1023
Tubal inflation, placenta previa following (Urdan), 142
insufflation, treatment of obstructed fallopian tubes in sterility by diathermy and (Mintz), 93
Tuberculosis and pregnancy (Royston, Jensen, and Hauptman), 284
Tubular adenoma (Pick), testicular (Miller), 680
Tucker-McLane forceps, modification of, to simplify their use and improve function and safety (Luikart), 686
Tumors, granulosa cell, malignancy of (Compton), 85
theca and lutein cell, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
lutein cell, theca and granulosa, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
malignant, effect of pregnancy on (Smith), 616
ovarian and parovarian, pregnancy complicated by (Wilson), 977
theca, granulosa and lutein cell, of human ovary and similar tumors of mouse's ovary (Traut and Butterworth), 987
Twin pregnancy analysis of 521 cases of (Guttmacher), 76
younger (Fruhinsholz), 638 (Abst.)

U

Ureterohydronephrosis resulting from pelvic inflammatory disease (Klempner), 125
Urethra, female, congenital obstructions of (Stevens), 84 (Abst.)
lymphogranuloma inguinale of (Gray), 247 (Abst.)
Urethral sphincter mechanism (Kennedy), 576
Urinary tract infections, end-results of, associated with pregnancy (Crabtree, Prather and Prien), 405
Urine and blood, hormonal studies of, abdominal pregnancy near term, operation and, with placenta left in situ (MacGregor), 1030
incontinence of (Kennedy), 576
Urology in women (Lewis), 337 (B. Rev.)
Uterine adnexa, endometriosis of (Barsony), 419 (Abst.)
bleeding in preclimacterium, treatment of (Joachimovits) 362 (Abst.)
hemorrhage, functional, treatment of (Keene and Payne), 688
prolapse, operation for, an efficient composite, and associated pathology (Richardson), 814
parametrial fixation operation for (Salmon), 58
Uterus, bicornuate, unilateral gonorrheal salpingitis in (James), 1045
body of, cancer of, after irradiation for metrorrhagia (Fournier) 355 (Abst.)
carcinoma of, diffuse squamous cell (Spielman), 159
modern treatment of (Dickinson), 355 (Abst.)
fibroid, pregnancy complicated by, triple diagnostic error in case of (Lucchetti), 1039 (Abst.)
fundus of, carcinoma of, experience in treatment of (Scheffey and Thudium), 1006
human (nonpuerperal), effect of ovarian hormones on (Krohn, Lackner, and Soskin), 379
nonpregnant human, study of contractions of (Robertson), 1047 (Abst.)
prolapse of (Baer, Reis, and Laemle), 827
sarcoma of (Novak and Anderson), 740

V

Vagina of pregnant and nonpregnant women, yeast-like fungi found in (Ch'in and Lim), 266 (Abst.)
Vaginal discharge (Renton), 1047 (Abst.)
Vascular factor in toxemias of late pregnancy (Eastman), 549
Viosterol and dicalcium-phosphate, bone changes in fetus following administration of, to pregnant mother (Finola, Trump, and Grimson), 955
Visscher-Bowman pregnancy test, chemical determination of (Drabkin and Goldschmidt), 634
experience with (Schenck and Tran), 526 (Correspondence)
Vitamine der Milch (Neuweiler), 177 (B. Rev.)
Von Hippel's disease complicated by pregnancy (Armstrong), 494
Vulva, carcinoma of, treatment of (Carranza), 357 (Abst.)
Vulvovaginal mycoses, biologic and clinical import of (Hesseltine), 855
experimental and clinical therapy of (Hesseltine), 439
Vulvovaginitis and oral thrush, cultural and morphologic studies of crytococci and monilias isolated from (Hopkins and Hesseltine), 209 (Abst.)

W

Washington Gynecological Society, transactions of, 529
Woman, married (Groves and Ross), 341 (B. Rev.)
single, and her emotional problems (Hutton), 340 (B. Rev.)